NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - UCB Pharma
   - Psoriasis and Psoriatic Arthritis Alliance
   - British Association of Dermatologists
   - Leo Pharma

3. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Hector Chinoy – clinical expert, nominated by UCB Pharma

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group critique of company**

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

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td>1</td><td>Company</td><td>UCB</td><td>

Section 3.10 (page 11)

Clinical benefits of CZP 400 mg Q2W dose escalation in patients with insufficient response to CZP 200mg Q2W

Key point 1: Clinical benefits of the CZP dose escalation

Section 3.10 (page 11) of the ACD states that "*When there is not a PASI 75 response to the 200 mg certolizumab pegol dose, there may be a response to an increased dose*".

UCB considers that this statement does not represent an accurate and full interpretation of the strength and breadth of the relevant evidence presented by UCB. UCB's response to the ERG clarification questions included further evidence, from the CIMPACT study, on the clinical benefit of increasing the dose to 400 mg Q2W in patients that initially received CZP 200 mg Q2W and either were PASI 50–74 responders (partial responders) at Week 16 (Table 1), or did not reach a PASI75 response (inadequate responders) at Week 16 (Table 2).

Among the CZP 200 mg Q2W partial responders (PASI 50–74) who escaped to CZP 400 mg Q2W (Table 1), with [redacted]% of patients achieving a PASI75 response rate and [redacted]% of patients achieving a PASI90 response rate at Week 32, ie within 16 weeks after dose escalation to 400mg Q2W. These response rates further increased by Week 48, to [redacted]% for PASI75, and [redacted]% for PASI90.[1]

Table 1: PASI responder rates at Week 32 and 48 in patients receiving CZP 200mg Q2W who at Week 16 achieved a PASI50 response, but not a PASI75 response (partial responders) and escaped to CZP 400 mg Q2W (CIMPACT study)

Responder rate, % (95% CI)	CZP 200 mg Q2W/Esc CZP 400 mg Q2W (n=[redacted])	
	Week 32	Week 48
PASI50	[redacted]	[redacted]
PASI75	[redacted]	[redacted]
PASI90	[redacted]	[redacted]
PASI100	[redacted]	[redacted]

Observed case.
Source: Company's response to the ERG clarification

</td><td>Thank you for your comments.

The clinical evidence section of the final appraisal document has been updated to focus on results in the partial response subgroup (see section 3.12), which is in alignment with considerations in the cost-effectiveness section (see section 3.22 and 3.23).</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Among CZP 200 mg Q2W patients who had an inadequate response (did not reach PASI75) at Week 16 and escaped to CZP 400 mg Q2W (Table 2), the majority ([redacted]%) achieved a PASI75 response at Week 32 (i.e. 16 weeks after dose escalation), and [redacted]%[i] of patients achieved a PASI90 response at Week 32. These responses further increased at Week 48 (i.e. 32 weeks after dose escalation) with [redacted]% of patients achieving a PASI75 response, and [redacted]% of patients achieving a PASI90 response.[2] Furthermore, among patients that achieve PASI 75 by Week 48 after escalating to CZP 400mg, 60% had already reached a PASI90 response by Week 48. **Table 2: PASI responder rates at Week 32 and 48 in patients receiving CZP 200mg Q2W who failed to achieve PASI75 response at Week 16 and escaped to CZP 400 mg Q2W (CIMPACT study)** **Responder rate, % (95% CI)** / **CZP 200 mg Q2W/Esc CZP 400 mg Q2W (n=[redacted])** **Week 32** / **Week 48** PASI50 [redacted] [redacted] PASI75 [redacted] [redacted] PASI90 [redacted] [redacted] PASI100 [redacted] [redacted] Non-responder imputation Source: Company's response to the ERG clarification [i]Value corrected/updated vs Table 34 of the UCB response to the ERG clarification questions. These results demonstrate that [redacted] of patients who achieve only a partial response at week 16 with CZP 200 mg Q2W go on to achieve a PASI75 response 16 weeks later by escalating to the higher dose of 400 mg Q2W, and furthermore that this response increases at 32 weeks after dose escalation. The ACD states that the Appraisal Committee is interested in receiving comments on whether all relevant data has been taken into account and whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. Based on the evidence provided above, UCB consider that the conclusions in Section 3.10 of the ACD do not adequately account for all of the relevant evidence submitted and that the conclusions regarding clinical effectiveness of CZP dose escalation are not reflective of the evidence available for the clinical efficacy of CZP dose escalation and are therefore not reasonable interpretations. UCB therefore requests that the Committee reconsiders their interpretation, summary and conclusions regarding the clinical efficacy of CZP dose escalation and revises the ACD wording accordingly and consequently reconsider the recommendation in Section 1.2. Further details of UCB's requested revisions to Section 1.2, in light of the clinical	

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			evidence presented in this Comment and discussions of the cost-effectiveness of the CZP escalation strategy in Comment 2, are detailed in Comment 6. ***Key point 2: Alignment of the discussion of the evidence base for clinical efficacy and cost-effectiveness of CZP escalation*** The discussion of clinical efficacy of CZP escalation in Section 3.10 of the ACD determines that patients who do not achieve a PASI75 response to CZP 200 mg Q2W could benefit clinically from dose escalation. In Section 3.21 (page 18), the ACD states that "*the cost effectiveness of the strategy of increasing the dose of certolizumab pegol in people with a partial response (defined as PASI 50 to a PASI 75) should be considered*". UCB notes that there is misalignment between Section 3.10 and Section 3.21 in terms of the evidence base discussed for the clinical efficacy and cost-effectiveness of CZP dose escalation: there is no discussion in Section 3.10 of the clinical benefit of dose escalation in patients with partial response (PASI 50 to PASI 75), although this is the patient group in which the cost-effectiveness of the CZP dose escalation strategy is then considered in Section 3.21. Clinical evidence in support of dose escalation in partial responders was provided by UCB as part of the response to ERG clarification questions and was used to inform the economic analysis discussed in Section 3.21 (as noted in key point 1 above). UCB thus consider that the clinical efficacy data in these subgroups should also be noted in Section 3.10, to ensure clarity over the available clinical evidence and the evidence base used to inform the economic analysis of dose escalation of CZP. UCB requests that the Appraisal Committee considers the evidence outlined in Key Points 1 and 2, as relevant and a suitable basis for guidance to the NHS, and further requests that it is accurately reflected in the ACD. UCB provide the below suggested revisions that we consider appropriately reflect the clinical evidence for CZP dose escalation and ensure alignment between the discussions of the clinical efficacy (ACD Section 3.10) and cost-effectiveness (ACD Section 3.21) for CZP escalation. **Suggested revisions, Section 3.10 (page 11)** • ***Current statement: "****When there is not a PASI 75 response to the 200 mg certolizumab pegol dose, there may be a response to an increased dose…The company presented clinical evidence showing that, if there is not a PASI 75 response after 16 weeks of treatment with a dosage of certolizumab pegol 200 mg every 2 weeks, there may be a response if this is increased to 400 mg every*	

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			2 weeks." ***Requested revision:*** ***"****When there is not a PASI 75 response to the 200 mg certolizumab pegol dose, there is an improved response to an increased dose…The company presented clinical evidence showing that, if there is not a PASI 75 response, or where there is a partial response (≥PASI 50 response but <PASI 75 response), after 16 weeks of treatment with a dosage of certolizumab pegol 200 mg every 2 weeks, there is a clinical response if this is increased to 400 mg every 2 weeks."*	

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2	Company	UCB	**Section 3.21, pages 18-19** *Cost-effectiveness of the CZP escalation strategy* Section 3.21 of the ACD presents the summary of the Committee's considerations regarding the economic analysis for CZP dose escalation (i.e. increasing the dose of CZP from 200mg Q2W to 400mg Q2W in patients with a partial response (defined as PASI 50 to a PASI 75) to CZP 200mg Q2W). The conclusion in the ACD is that the CZP dose escalation strategy is not cost-effective. Furthermore, as indicated in the ACD, the ERG considered that in addition to the comparison to alternative comparator dose escalation strategies, the CZP dose escalation strategy should have been compared to strategy of switching to a next biological treatment. While UCB's submitted economic analysis and conclusion (CZP dose escalation being more effective and less costly than ADA escalation strategy) are briefly mentioned, the ACD indicates that the Committee conclusion is based on the sole consideration of the results of the ERG analysis, which is noted to have an ICER over £500,000 per QALY gained. UCB considers that the Committee conclusion is not based on a full and thorough consideration of clinically relevant comparisons and all available evidence. In this context, and given the proven clinical benefits associated with the increase of the CZP dose to 400mg Q2W (as per the submitted evidence, re-emphasised in Comment 1 earlier in this response) and the clear clinical desire for the possibility to escalate CZP in clinical practice (as noted in Section 3.10 of the ACD), UCB considers that conclusions regarding the cost-effectiveness of CZP escalation should be based on a full appraisal of the various potential approaches and the resulting balance of evidence. UCB would like to raise a number of points of concern which should be considered at the second Appraisal Committee meeting, summarized in Section 1 below. Firstly, UCB would like to highlight an apparent error in the ACD reporting of the analysis on which the Committee decision appears to be based (i.e. the analysis producing an ICER >£500,000 per QALY gained). Secondly. UCB highlight a key concern with the exclusion from consideration of clinically relevant comparisons of the CZP dose escalation strategy, which results in a Committee decision that is based on a single analysis and not full consideration of the health economic evidence. Finally, UCB raise a consideration regarding a potential source of bias in the analysis on which the Committee decision has been based. These concerns are presented in more detail in Section 1 below. Based on these concerns, UCB provide an overview of ICERs from a range of additional	Comments noted.

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			cost-effectiveness analyses evaluating CZP dose escalation, taking on board previous ERG and NICE Committee comments as to preferred modelling approaches (Section 2 below). From these analyses it is clear that the choice of the comparator for the CZP dose escalation has a notable effect on the estimated true relative treatment costs associated with CZP dose escalation and hence the conclusions regarding cost-effectiveness. Nevertheless, the conclusions of these new scenario analyses support the cost-effectiveness of the CZP dose escalation with the current PAS. Furthermore, it is also clear that consideration of [redacted] As such, on the balance of the available evidence it is reasonable to conclude that CZP dose escalation can provide a cost-effective treatment option to the NHS for the treatment of adults with moderate to severe plaque psoriasis. Consequently, UCB considers that this new evidence is relevant for consideration at the second Appraisal Committee meeting to inform the Committee recommendations with respect to the potential use of the CZP dose escalation (ACD recommendation 1.2). **1. <u>Points of concern with the analysis on which the Committee preliminary decision regarding CZP dose escalation</u>** ***Incorrect reporting of the ICER for CZP dose escalation in the ACD*** The ERG analysis producing an ICER over £500,000 per QALY gained is stated in the ACD to be based on comparison of the following sequences (Section 3.21, page 18): • *CZP 200mg→CZP 400mg→UST 90mg→IFX→BSC* • *CZP 200mg→UST 90mg→IFX→BSC* UCB believe this is incorrect. Following the review of the ERG version of the UCB submitted model, running the above sequence results in an ICER of £122,560.18. The only ICER relating to the dose escalation analysis that is >£500,000 per QALY gained, mentioned in the ERG report addendum (£533,154 per QALY gained), is based on the following sequences: • *CZP 200mg→CZP 400mg→BSC→BSC→BSC* • *CZP 200mg→UST 90mg→BSC→BSC→BSC* UCB therefore believes that the ACD should be revised to accurately reflect the	NICE acknowledges that the treatment sequences presented in the appraisal consultation document were incorrect and should have referred to the following sequences: • *CZP 200mg→CZP 400mg→BSC→BSC→BSC* • *CZP 200mg→UST 90mg→BSC→BSC→BSC* This error did not affect the conclusions of the appraisal consultation document.

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			sequences considered by the ERG in relation to this ICER. Regardless of this error in reporting, UCB acknowledge that the ICER resulting from either sequence is above conventional NICE cost-effectiveness thresholds. However, UCB consider that drawing conclusions from this single ICER as it is reported in the ACD does not constitute a full and thorough consideration of clinically relevant comparisons and all available evidence. ***Decision based on a single analysis and not full consideration of the health economic evidence*** UCB maintain that the relevant comparison to a strategy of CZP dose escalation is to an alternative escalation strategy of ADA. This is because the CZP escalation strategy considers the case where an escalation strategy to a higher dose of the existing treatment is considered the most appropriate clinical course of action if possible. The most relevant comparison is therefore to the currently available treatment option for clinicians wishing to follow a treatment strategy of maintenance on the existing therapy through escalation (rather than having to undergo a switch to a different treatment option, which may be felt to be clinically less appropriate, particularly in the case where patients have obtained partial response to their initial treatment). The appropriate comparison is therefore a comparison to ADA escalation, which is licensed for a dose increase in the case of inadequate response. As such, UCB wish to re-iterate the relevance of the revised base case analysis submitted in the proforma response to the ERG report (UCB proforma response appendices, Table 6), which represent the latest base case. UCB acknowledge that the ACD states that. "…*in addition to being compared with a different dose escalation strategy, the dose escalation sequence should also be compared with switching to the next biological treatment in the treatment pathway*" (ACD, Section 3.21). However, when considering switch strategies as comparators the ACD currently fails to acknowledge that a switch to UST 90mg is not the only switch that might be considered clinically appropriate. Guselkumab and brodalumab are relatively recently approved for use in the NHS and do not currently represent the standard clinical practice for a second-line therapy; however, it is very plausible in practice that a clinician may consider secukinumab or ixekizumab, as alternative options to UST 90mg, as second-line therapy switch therapy in patients for whom CZP does not provide a sufficient response. Therefore, UCB consider that any evaluation of CZP dose escalation versus a switch	The company's updated analyses were considered by the committee. Please see section 3.22 and 3.23 of the final appraisal document.

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strategy should consider the results of economic analyses across other potentially relevant switch strategies, and not be based solely on the single comparison to a switch to UST 90mg.

Source of bias in the single analysis considered by the Committee

In the ERG's analysis, the efficacy data over the first two lines of therapy (i.e. CZP 200mg→CZP 400mg, or CZP 200mg→UST 90mg) is modelled by the ERG as follows:

Table 3: Efficacy sources for modelling 1st line and 2nd line in the ERG's dose escalation analysis presented in the ACD (ICER >£500,000 per QALY gained)
<table>
<tr><th></th><th>CZP dose escalation strategy
(CZP 200mg > CZP 400mg > BSC > BSC > BSC)</th><th>"Switch" to UST 90mg strategy
(CZP 200mg > UST90 > BSC > BSC > BSC)</th></tr>
<tr><td>1st line</td><td>CZP 200mg efficacy based on results of NMA</td><td>CZP 200mg efficacy based on results of NMA</td></tr>
<tr><td>2nd line</td><td>CZP 400mg efficacy based on weighted average of:

• For the proportion of patients considered to be partial responders (PASI 50-74) to CZP 200mg: clinical data provided by UCB for efficacy of CZP 400mg in the population of partial responders (PASI 50-74) to CZP 200mg from the CIMPACT study
• For the proportion of patients considered to be non-responders (PASI <50) to CZP 200mg: UST 90mg efficacy based on results of NMA, in order to model that non-responders to CZP 200mg would switch to UST 90mg rather than escalate</td><td>UST 90mg efficacy based on results of NMA</td></tr>
</table>
Source: Section 5.2 (ERG report)/Section 5.2 (ERG Report Addendum) describe the sequences compared. Efficacy sources determined through review of the ERG model.

Considering each treatment arm in isolation, the above choices of efficacy sources initially appear reasonable. For CZP dose escalation, clinical data for efficacy of CZP
</td><td>The company's updated scenario analyses were considered by the committee. Please see section 3.22 and 3.23 of the final appraisal document.</td></tr>
</table>

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			400mg as escalation is available and it is therefore logical to utilise this. For the switch to UST90mg, it is assumed that the NMA-derived efficacy holds for the use of UST 90mg as a second-line therapy. This implicitly assumes that UST 90mg has the same efficacy when used as a 1st line treatment as when used at 2nd line. This potentially inflates the efficacy of UST 90mg in the 2nd-line, as it would be expected that efficacy of biologics would decrease with each line of therapy. Such an assumption – whereby an NMA used to inform 1st-line efficacy is used to model 2nd and later-line efficacy – is common practice in the absence of any more appropriate data, and commonly the bias resulting from this potential efficacy inflation is limited in nature because the same assumption applies in all model arms. However, in the analysis of the ERG described above this inflated efficacy does not apply equally to both arms, because in the CZP escalation arm it is data from the CIMPACT study and not from the NMA that is used to model treatment efficacy of CZP 400mg as a 2nd-line treatment in patients who have responded only partially to CZP 200mg. As such, the approach to modelling efficacy that is outlined in Table 3 introduces a bias, and this bias is not acknowledged by the ERG or the Committee in the ACD. The impact of this bias can be explored by using the same efficacy source in both treatment arms. ***Summary of concerns*** In summary, UCB consider that it is inappropriate to base decisions regarding the cost-effectiveness of CZP dose escalation on a single analysis comparing a CZP escalation strategy to a "switch" to UST 90mg strategy as it is currently reflected in the ACD. The most appropriate comparison is to a dose escalation strategy of ADA 40mg to ADA 80mg. Acknowledging that the ERG take a differing view and consider comparisons to a switch strategy to be more appropriate, the decision should be based on balanced consideration across the range of potentially relevant comparisons, including both comparisons to an ADA escalation strategy and comparisons to switch strategies. In addition, the impact of the source of bias in the ERG's current analysis should be considered for decision-making. 2. **<u>New analyses supporting the cost-effectiveness of CZP dose escalation</u>** Given the above, UCB present results from a number of new scenario analyses supporting the cost-effectiveness of the CZP dose escalation strategy that are relevant to be considered by the Appraisal Committee at the second meeting. In doing so, UCB have taken into account previous considerations of the ERG and the Committee, as outlined in Section 3.18 of the ACD, that "…*treatment sequences, although more likely*	

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			to reflect the treatment switching seen in clinical practice, may have provided misleading cost-effectiveness estimates for certolizumab pegol". The ACD notes that to address these issues the ERG performed analyses setting subsequent options in sequences to best supportive care. Therefore, UCB has provided analyses both with treatment sequencing and removing treatment sequencing (i.e. all subsequent treatment options set to BSC after the escalated therapy/switch biologic) in order to assess the influence of treatment sequencing on results. The analyses for which results are provided are outlined in Table 4 below. Firstly, UCB maintain that the comparison to ADA escalation is the appropriate comparison and therefore re-iterate the revised base case from the UCB proforma response to the ERG report, which represents the latest base case. Subsequently, the concerns raised in Section 1 above are addressed through the presentation of additional analyses that: • consider additional comparisons to other switch strategies (SEC, IXE) *and* • explore the impact of the potential source of bias by aligning efficacy sources between the CZP escalation and comparator arms. Two conservative approaches are explored, which in both cases consider the separate populations of partial responders (PASI50-74) and non-responders (PASI<50) to initial therapy and align the sources of efficacy for these populations as appropriate between the CZP escalation and comparator arms: 1. For partial responders: the efficacy estimates of the 2nd line biologic treatment comparator is assumed to be the same as the clinical efficacy data of CZP 400mg in the population of partial responders (PASI 50-74) from the CIMPACT study 2. For non-responders: the efficacy estimate for both the CZP 400mg and the comparator is assumed to be based on the respective NMA estimates for the therapy received by partial and non-responders A detailed description of the approach to efficacy alignment is provided in **Error! Reference source not found.** to this response. With the exception of the above adjustments for efficacy sources and the sequences	

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modelled, the new scenario analyses presented in this response are based on the same model and assumptions considered for the UCB latest base case cost-effectiveness results for the CZP escalation strategy, included in the pro forma response to the ERG report (UCB proforma response, Table 6). A summary of the sequences modelled for the new scenario analyses below versus the approach in the UCB latest basecase (response proforma) and the ERG's approach that gave rise to the ICER quoted in the ACD is provided in Error! Reference source not found..

Table 4: Summary of presented analyses
<table>
<tr><th>Analysis</th><th>Notes</th></tr>
<tr><td colspan="2">Base case analysis</td></tr>
<tr><td>UCB proforma response analysis

(CZP escalation vs ADA escalation – sequences)</td><td>The updated base case analysis for the PASI 50-74 response at Week 16 group, provided in Table 6 of the UCB proforma response appendix.</td></tr>
<tr><td colspan="2">Additional scenario analyses</td></tr>
<tr><td>1. CZP escalation vs ADA escalation – sequences</td><td>This analysis is the same as the base case analysis but explores the efficacy adjustment described above</td></tr>
<tr><td>2. CZP escalation vs ADA escalation – no sequences</td><td>This analysis is the same as the base case analysis but explores the efficacy adjustment described above and removes treatment sequencing</td></tr>
<tr><td>3. CZP escalation vs switch to SEC – sequences</td><td>New analysis that explores the efficacy adjustment described above and considers the comparison to a switch to SEC strategy</td></tr>
<tr><td>4. CZP escalation vs switch to IXE – sequences</td><td>New analysis that explores the efficacy adjustment described above and considers the comparison to a switch to IXE strategy</td></tr>
<tr><td>5. CZP escalation vs switch to SEC – no sequences</td><td>As above switch to SEC analysis, but removing treatment sequencing</td></tr>
<tr><td>6. CZP escalation vs switch to IXE – no sequences</td><td>As above switch to IXE analysis, but removing treatment sequencing</td></tr>
<tr><td>7. CZP escalation vs switch to UST – no sequences</td><td>This analysis is the same as the switch to SEC and switch to IXE analyses above but models a switch to UST 90mg instead, similarly to the latest ERG analysis quoted in the ACD. This analysis is the same as the ERG analysis that gives rise to the</td></tr>
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</td><td></td></tr>
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			<table><tr><td></td><td>ICER >£500k (quoted in the ACD) but explores the impact of the efficacy adjustment.</td></tr></table> It should be noted that all analyses of CZP dose escalation presented to date may inflate the costs associated with CZP 400mg, and this remains a limitation of the revised analyses presented below. To model the CZP escalation sequence, CZP 400mg Q2W is modelled as the second-line treatment in the sequence in order to fit with the model structure. This means that all patients who are initially responders to 1st line CZP 200mg Q2W, who continue to maintenance CZP 200mg and who then discontinue maintenance therapy currently move to receive escalated CZP 400mg in the model. This discontinuation of CZP 200mg Q2W maintenance therapy is based on the 20% annual withdrawal rate assumption for the maintenance period of biologics and captures discontinuation both due to loss of efficacy and due to adverse events. While patients who withdraw from CZP 200mg maintenance due to loss of efficacy may well be considered for dose escalation, patients who withdraw due to adverse events on CZP 200mg would not be escalated in clinical practice to CZP 400mg. These patients would likely instead move to a different biologic. However, the model structure currently does not allow this: patients who discontinue from their 1st line maintenance therapy must move to the 2nd line therapy in the sequence (which is CZP 400mg Q2W in the CZP escalation arm). As such, the model currently inflates the use of CZP 400mg by the proportion of patients who would discontinue maintenance CZP 200mg due to adverse events. The same limitation applies to comparator escalation sequences (i.e. costs of ADA escalation are similarly inflated due to the same model limitation) and so this is not a relevant concern for the comparison to alternative escalation strategies. However, because there is no inflation of costs in the comparator arm for the comparisons to switch strategies (it is accurate to assume that patients discontinuing maintenance CZP 200mg due to both loss of efficacy and adverse events would switch to a new biologic), this limitation means that the ICERs presented below for CZP escalation versus the switch strategies may be conservative. The results of the set of analyses that UCB believe should be considered in full to inform decision-making are presented below in Table 5 (re-iteration of the UCB base case analysis) and Table 6 (results of new scenario analyses, including comparisons to alternative switch strategies and exploration of efficacy adjustments). Full tables of results (detailing total and incremental costs and QALYs in addition to ICERs) are provided in Appendix 3 to this response. The analyses conducted provide results across a broad range of possible comparisons	This limitation in the model structure was considered by the committee. Please see section 3.23 of the final appraisal document.

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			and indicate the following: • CZP dose escalation is cost-effective in 11/15 analyses, with the only exceptions being the comparison to ADA escalation without sequencing and the comparison to a switch to UST strategy, highlighting that the ERG ICER quoted in the ACD is not representative of the full spectrum of plausible cost-effectiveness results for CZP escalation. • The analysis conducted by the ERG and referenced in the Committee decision-making in the ACD (i.e. the comparison to switch to UST 90mg) represents the most pessimistic ICER amongst 15 clinically plausible comparisons and therefore does not reflect a balanced consideration of the evidence. • Results are generally robust to the exploration of alternative efficacy assumptions. Whilst each of the two assumptions explored is associated with inherent limitations regarding the validity of the necessary assumptions, this should provide confidence that the results of the analyses are generally robust to exploration of the source of bias in the efficacy assumptions that is described above. Of interest, when addressing the source of bias in the efficacy assumption by using the NMA efficacy in both treatment arms, the ICER for the comparison to the switch to UST 90mg (the equivalent of the ERG ICER quoted in the ACD) drops considerably. • In the majority of analyses, differences in incremental QALYs are small, indicating relative stability of the estimates of incremental benefit of the CZP dose escalation. This highlights that the uncertainty relates primarily to the estimation of the incremental costs associated with CZP escalation. It should also be noted that the high ICER in the comparison to the switch to UST 90 is a product of small incremental QALYs. Consideration of the cost-effectiveness results across the range of potentially relevant comparisons presents a considerably different case for the cost-effectiveness of CZP escalation compared to that presented in the ACD, which is based on consideration of a single ICER. Consequently, UCB believe that the results included in this response should be considered in the second Appraisal Committee meeting and the Committee decision, to ensure all relevant evidence has been accounted for. UCB acknowledge that when considering the range of analyses presented below supporting the cost-effectiveness of the CZP dose escalation, uncertainty still remains regarding the true incremental costs of increasing the dose of CZP. Therefore, results where [redacted] are	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
presented in Table 7 (re-iteration of the UCB latest base case analysis) and Table 8 (results of new scenario analyses, including comparisons to alternative switch strategies and exploration of efficacy adjustments). Full detailed results are provided in Error! Reference source not found.. Under this assumption, CZP escalation becomes the cost-effective treatment strategy across all analyses, reducing uncertainty over true treatment costs for increasing the dose from 200 mg to 400mg of certolizumab pegol. [redacted], considering the clinical desire to have an option to escalate to CZP 400mg Q2W that was acknowledged both at the 1st Appraisal Committee meeting and in the ACD (Section 3.10). It is important to note that in a previous appraisal considering dose escalation for infliximab and adalimumab in the context of Crohn's disease (NICE TA187), it was ultimately noted that "the Committee remained uncertain about true treatment costs for infliximab and adalimumab and accepted that local arrangements would have an impact on relative costs". The analyses presented in this response reflect a similar situation where there is clear clinical desire for dose escalation and uncertainty around true treatment costs depending on the specific analysis considered to assess the cost-effectiveness of the dose escalation. The additional analyses accounting for [redacted] clearly indicate that CZP is a cost-effective treatment option across all analyses considered [redacted], further supporting the conclusions of the cost-effectiveness analyses of the CZP dose escalation with the agreed PAS. On this basis, UCB would consider that similar wording would be appropriate for the case of dose escalation from CZP 200mg to CZP 400mg in Section 3.21 of the ACD.

Table 5: Latest base case cost-effectiveness results for CZP escalation strategy (CZP with PAS)

<table>
<tr><th rowspan="2">First-line therapy</th><th rowspan="2">Subsequent sequence</th><th colspan="2">Total</th><th colspan="2">Incremental</th><th rowspan="2">ICER</th></tr>
<tr><th>QALYs</th><th>Costs</th><th>QALYs</th><th>Costs</th></tr>
<tr><td colspan="7">Efficacy assumptions for CZP (PASI 50-74 response at week 16)</td></tr>
<tr><td>CZP 200mg</td><td>CZP400mg, UST, IFX, BSC</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td></tr>
<tr><td>ADA 40mg</td><td>ADA80mg, UST, IFX, BSC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>CZP dominates</td></tr>
</table>

Source: Table 6, Appendix of UCB Pro Forma Response to ERG report.

Table 6: New cost-effectiveness scenario analyses for CZP escalation strategy (CZP with PAS)
</td><td>The committee was unable to consider the company's proposed commercial arrangement [redacted]. Please see section 5.5.2 of 'Guide to the methods of technology appraisal (2013).'</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Comparison	First-line therapy	Subsequent sequence	ICER Aligning to CZP 400mg CIMPACT partial responders efficacy	ICER Aligning to NMA efficacy
Comparison to ADA escalation				
Modelling sequences of treatments				
CZP escalation	CZP 200mg	CZP 400mg, UST 90mg, IFX, BSC	-	-
vs ADA escalation	ADA 40mg	ADA 80mg, UST 90mg, IFX, BSC	£22,370	£28,354
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)				
CZP escalation	CZP 200mg	CZP 400mg, BSC, BSC, BSC	-	-
vs ADA escalation	ADA 40mg	ADA 80mg, BSC, BSC, BSC	£35,481	£39,489
Comparison to switch strategies				
Modelling sequences of treatments				
CZP escalation	CZP 200mg	CZP 400mg, UST 90mg, IFX, BSC	-	-
Switch to SEC	CZP 200mg	SEC, UST 90mg, IFX, BSC	£147,965 (SW*)	£134,435 (SW*)
Switch to IXE	CZP 200mg	IXE, UST 90mg, IFX, BSC	£200,461 (SW*)	£132,245 (SW*)
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)				
CZP escalation	CZP 200mg	CZP 400mg, BSC, BSC, BSC	-	-
Switch to SEC	CZP 200mg	SEC, BSC, BSC, BSC	£148,126 (SW*)	£133,868 (SW*)
Switch to IXE	CZP 200mg	IXE, BSC, BSC, BSC	£201,308 (SW*)	£130,462 (SW*)

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Switch to UST 90mg	CZP 200mg	UST90, BSC, BSC, BSC	£523,460	£313,525

*SW indicates a south-west ICER (i.e. CZP escalation strategy associated with lower QALYs and lower costs. These ICERs have been presented as the ICER for the comparator sequence versus the CZP escalation sequence for ease of interpretation. Therefore, SW ICERs above £30,000 indicate that the CZP escalation strategy is cost-effective at conventional thresholds.

Table 7: Latest base case cost-effectiveness results for CZP escalation strategy ([redacted])

First-line therapy	Subsequent sequence	Total		Incremental		ICER
		QALYs	Costs	QALYs	Costs	
CZP 200mg	CZP 400mg, UST, IFX, BSC	[redacted]	[redacted]			
ADA 40mg	ADA 80mg, UST, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	CZP dominates

Source: Table 6, Appendix of UCB Pro Forma Response to ERG report.

Table 8: New cost-effectiveness scenario analyses for CZP escalation strategy ([redacted])

Comparison	First-line therapy	Subsequent sequence	ICER Aligning to CZP 400mg CIMPACT partial responders efficacy	ICER Aligning to NMA efficacy
Comparison to ADA escalation				
Modelling sequences of treatments				
CZP escalation	CZP 200mg	CZP 400mg, UST 90mg, IFX, BSC	-	-
vs ADA escalation	ADA 40mg	ADA 80mg, UST 90mg, IFX, BSC	CZP dominates	CZP dominates
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)				
CZP escalation	CZP 200mg	CZP 400mg, BSC, BSC, BSC	-	-
vs ADA escalation	ADA 40mg	ADA 80mg, BSC, BSC, BSC	CZP dominates	CZP dominates
Comparison to switch strategies				

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
<table>
<tr><td colspan="5">Modelling sequences of treatments</td></tr>
<tr><td>CZP escalation</td><td>CZP 200mg</td><td>CZP 400mg, UST 90mg, IFX, BSC</td><td>-</td><td>-</td></tr>
<tr><td>Switch to SEC</td><td>CZP 200mg</td><td>SEC, UST 90mg, IFX, BSC</td><td>£944,479 (SW*)</td><td>£857,370 (SW*)</td></tr>
<tr><td>Switch to IXE</td><td>CZP 200mg</td><td>IXE, UST 90mg, IFX, BSC</td><td>£884,443 (SW*)</td><td>£521,948 (SW*)</td></tr>
<tr><td colspan="5">Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)</td></tr>
<tr><td>CZP escalation</td><td>CZP 200mg</td><td>CZP 400mg, BSC, BSC, BSC</td><td>-</td><td>-</td></tr>
<tr><td>Switch to SEC</td><td>CZP 200mg</td><td>SEC, BSC, BSC, BSC</td><td>£948,659 (SW*)</td><td>£844,154 (SW*)</td></tr>
<tr><td>Switch to IXE</td><td>CZP 200mg</td><td>IXE, BSC, BSC, BSC</td><td>£891,737 (SW*)</td><td>£495,350 (SW*)</td></tr>
<tr><td>Switch to UST 90mg</td><td>CZP 200mg</td><td>UST90, BSC, BSC, BSC</td><td>£19,229</td><td>£23,760</td></tr>
</table>
*SW indicates a south-west ICER (i.e. CZP escalation strategy associated with lower QALYs and lower costs. These ICERs have been presented as the ICER for the comparator sequence versus the CZP escalation sequence for ease of interpretation. Therefore, SW ICERs above £30,000 indicate that the CZP escalation strategy is cost-effective at conventional thresholds.
</td><td></td></tr>
</table>

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3	Company	UCB	**Section 3.20 (page 17):** Within Section 3.20 (page 17), the Committee states that *"…people with psoriasis, particularly those whose psoriasis does not respond to adalimumab, would value the option of an alternative TNF-alpha inhibitor."* UCB would like to note that the key clinical data and economic analysis for certolizumab pegol provided in the Company Submission related to the population of patients who were inadequate responders to systemic non-biologic therapy or candidates for systemic non-biologic, as per the marketing authorisation and the final NICE scope. Furthermore, for the inadequate responders to systemic non-biologic therapy population, the evidence included in the Company Submission was supportive of the requested positioning for CZP in the treatment pathway, in line with recommendation of other biologics for the treatment of moderate to severe plaque psoriasis, as a first-line biologic treatment option, which was agreed by the Committee, as noted in Section 3.3 of the ACD. UCB would like to note that the wording in Section 3.20 of the ACD does not accurately reflect the evidence submitted and considered by the Appraisal Committee for the appraisal of CZP in terms of the appropriate positioning of CZP. UCB considers that the statement in the ACD is not a reasonable interpretation of the evidence and the committee discussions, and therefore requests the removal of this wording from the ACD as per the suggested revised wording below. **Suggested revisions, Section 3.20 (page 17)** • **Current statement: "***The committee agreed that people with psoriasis, particularly those whose psoriasis does not respond to adalimumab, would value the option of an alternative TNF-alpha inhibitor that was more effective than etanercept and…*" **Requested revision: "***The committee agreed that people with <u>psoriasis would value the option of an alternative TNF-alpha inhibitor</u> that was more effective than etanercept and…*"	Comment noted. The text has been amended. See section 3.21 of the final appraisal document.
4	Company	UCB	**Section 3.11 (page 11, 12).** <u>Certolizumab pegol molecular structure and difference between biologics</u> ***Key point 1: Existence of relevant clinical data*** In Section 3.11 (page 11, 12) of the ACD, the Appraisal Committee highlights that, in light of the structure of certolizumab pegol (CZP), this drug "*would not be anticipated to*	Comments noted. The text has been removed. Please see section 3.25 of the final appraisal document for the committee's conclusions on the use of certolizumab pegol during pregnancy and breastfeeding.

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			cross the placenta". While this statement is valid, UCB would like to note that this hypothetical phrasing is not commensurate with the existence of data from the CRIB pharmacokinetic study of 16 pregnant women receiving CZP 200 mg every two weeks (Q2W) or CZP 400 mg every four weeks (Q4W), which provides clinical evidence that there is no to minimal placental transfer of CZP from mothers to infants.[5] The Summary of Product Characteristics for CZP reflects the findings of the CRIB study by referencing that there is "low or negligible placental transfer". UCB therefore requests that Section 3.11 is updated to better reflect the availability of these clinical data and the extent to which the behaviour of CZP with regards to placental transfer is known and underpinned by evidence, including a statement on the conclusions of the evidence from CRIB and CRADLE. ***Key point 2: Differences between the anti-TNFs*** In Section 3.11 of the ACD, it is highlighted that "*The clinical experts stated that these data were consistent with the structure of certolizumab pegol, which would not be anticipated to cross the placenta. They considered certolizumab pegol could be used in pregnancy if needed and while breastfeeding. The only other biological treatment with a summary of product characteristics stating that it can be used in pregnancy and breastfeeding is adalimumab, while infliximab's summary of product characteristics states that it can be used during in breastfeeding*". UCB considers that the current summary of the evidence could be confusing and misleading, and requests certain revisions to this section to ensure a full context is provided of the existing evidence. Considering the conclusions of the clinical experts regarding the molecular structure of certolizumab pegol, the use of the wording "*The only other biological treatment*…" in the context of the preceding discussion suggests a resemblance or similarity between CZP and adalimumab, which could be incorrectly interpreted as suggesting that the structural elements of the CZP molecule that result in no to minimal placental transfer are shared by adalimumab. This is not the case: active transport of immunoglobulin G (IgG) across the placenta (occurring predominantly during the second and third trimesters of pregnancy)[5] is mediated by the neonatal fragment crystallisable (Fc) receptor (FcRn).[6] CZP has a unique molecular structure amongst biologics in lacking this Fc region, meaning it does not bind FcRn.[5, 7] While certolizumab pegol, adalimumab and infliximab are anti-TNFs, they do not share the same molecular structure, which is a critical element with respect to the active transport of immunoglobulin G (IgG). Furthermore, the current wording in the above statements from Section 3.11 may be incorrectly interpreted as suggesting that adalimumab and infliximab are not anticipated	

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			to undergo maternal to fetal placental transfer, given the current flow of Section 3.11 and the way that reference to these products follows on directly from the discussion of no to minimal CZP placental transfer and the linking of this to use of CZP in pregnancy and breastfeeding. However, in a study of pregnant women with Crohn's disease receiving anti-TNF treatment, the median ratio of cord to maternal drug level on the day of birth was 160% for infliximab, and 179% for ADA. In contrast, the median ratio of cord to maternal CZP level was 3.9%.[8] UCB would also like to note that the latest European Summary of Product Characteristics for both adalimumab (Humira®) and infliximab (Remicade®) report that these anti-TNFs may (adalimumab) or do (infliximab) cross the placenta, as indicated below: "*Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy*."[9] *"Infliximab crosses the placenta and has been detected in the serum of infants up to 6 months following birth*."[10] The latest Summary of Product Characteristics for certolizumab pegol states that "*Non-clinical studies suggest low or negligible level of placental transfer of a homologue Fab-fragment of certolizumab pegol (no Fc region)".* Other differences in Summary of Product Characteristics wording exist for CZP compared to adalimumab and infliximab in relation to women of childbearing potential and breastfeeding. Finally, according to the ACD, "*infliximab's summary of product characteristics states that it can be used during in breastfeeding*". However, UCB would like to highlight that infliximab's summary of product characteristics in fact states that "Infliximab should only be used during pregnancy if clearly needed", and that *"women must not breast feed for at least 6 months after Remicade treatment"*.[10] UCB thus considers it important that the ACD accurately reflects the difference between the molecules and the link between the molecular structure and use in women of childbearing potential, as well as pregnant and breastfeeding women, to ensure there is no risk of ambiguity by implying that these biologics are associated with identical considerations for these patients. UCB therefore requests that Section 3.11 is revised to make clear that the structure of CZP and the resulting impact on placental transfer from mothers to infants[5] are unique to CZP and that this section is reworded to avoid any ambiguity or potential for confusion in relation to any Summary of Product Characteristics, specifically any supporting or underlying evidence, data or findings around pregnancy and breastfeeding.	NICE acknowledges that the appraisal consultation document incorrectly stated that '*infliximab's summary of product characteristics states that it can be used during in breastfeeding'* This should have instead stated that infliximab can be used in pregnancy if clearly needed.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			UCB's suggested revisions to Section 3.11 of the ACD, addressing the above key points 1 and 2 are listed below (text underlined): **Suggested revisions, Section 3.11 (page 11, 12):** • **Current statement:** *"The summary of product characteristics for certolizumab pegol states that it can be used during pregnancy and breastfeeding. The evidence for this was based on 2 clinical studies (CRIB and CRADLE) and safety registry data collected on certolizumab pegol across its licensed indications. The clinical experts stated that these data were consistent with the structure of certolizumab pegol, which would not be anticipated to cross the placenta. They considered certolizumab pegol could be used in pregnancy if needed and while breastfeeding. The only other biological treatment with a summary of product characteristics stating that it can be used in pregnancy and breastfeeding is adalimumab, while infliximab's summary of product characteristics states that it can be used during in breastfeeding. The patient experts explained that people who are pregnant or who are considering pregnancy would welcome further effective treatment options for plaque psoriasis that do not need to be stopped before and during pregnancy, or while breastfeeding."* • **Requested revision:** *"The summary of product characteristics for certolizumab pegol states that it can be used during pregnancy and breastfeeding. The evidence for this was based on 2 clinical studies (CRIB and CRADLE) and safety registry data collected on certolizumab pegol across its licensed indications. The CRIB study demonstrated no to minimal maternal-to-fetal placental transfer of CZP, while the CRADLE study demonstrated minimal transfer of CZP into breast milk. The clinical experts stated that these data were consistent with the structure of certolizumab pegol (Fc-free), which would not be anticipated to cross the placenta. They considered certolizumab pegol could be used in pregnancy if needed and while breastfeeding. The only other biological treatment with a summary of product characteristics stating that it can be used in pregnancy and breastfeeding is adalimumab, while infliximab's summary of product characteristics states that it can be used during pregnancy only if clearly needed, and that women should not breastfeed for up to 6 months after treatment. However, the summary of product characteristics for adalimumab and infliximab indicate that these may or do cross the placenta. The patient experts explained that people who are pregnant, considering pregnancy or breastfeeding would welcome an effective treatment option for plaque psoriasis that does not need to be stopped before and during pregnancy, or while*	

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			breastfeeding."	

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5	Company	UCB	**Section 3.24 (page 21)** In Section 3.11, the Appraisal Committee reports that "*The patient experts explained that people…would welcome further effective treatment options for plaque psoriasis that do not need to be stopped before and during pregnancy, or while breastfeeding*." However, in Section 3.24 (page 21), it is noted that "*The committee understood that people would welcome an additional treatment option that can be used during pregnancy and the pre-conception period*." UCB considers that the section on Equality issues should be aligned with section 3.11 and also indicate the need for a treatment that can be used during breastfeeding (acknowledged by the Appraisal Committee in Section 3.11). UCB would thus request that Section 3.24 and Section 3.11 of the ACD are aligned to fully reflect the holistic needs among women of child-bearing age with psoriasis, i.e. a treatment option that can be used during the pre-conception period, during pregnancy, *and* while breastfeeding. **Suggested revisions, Section 3.24 (page 21):** • **Current statement: "***The committee understood that people would welcome an additional treatment option that can be used during pregnancy and the pre-conception period."* **Requested revision:** "*The committee understood that people would welcome a treatment option that can be used during pregnancy (if clinically needed), the pre-conception period, and breastfeeding."*	Comment noted. The text has been amended. Please see section 3.25 of the final appraisal document.
6	Company	UCB	**Section 1.2 (page 3)** In light of the previous comments and evidence presented by UCB in this document in relation to dose escalation for certolizumab pegol from both a clinical and cost-effectiveness standpoint, UCB asks that the ACD reconsiders the recommendations in Section 1.2 (page 3), as well as the supporting rationale provided in Section 3.22 (page 19). Specifically, as detailed in Comment 1, data from the CIMPACT study show that, when there is not a PASI75 response to certolizumab pegol 200 mg, there is an improved response to certolizumab pegol 400 mg: [redacted]% of patients who achieve only a partial response at week 16 with CZP 200 mg Q2W go on to achieve a PASI75 response 16 weeks later by escalating to the higher dose of 400 mg Q2W. Furthermore, this response increases at 32 weeks after dose escalation. UCB acknowledge that when considering the range of analyses presented as part of Comment 2, supporting the cost-	Comment noted. The additional evidence presented by the company has been considered by committee. No changes have been made to the recommendations. Please see sections 1.1, 1.2, 3.12, 3.22 and 3.23 of the final appraisal document.

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			effectiveness of the CZP dose escalation strategy, uncertainty might remain regarding the true incremental costs of CZP escalation. To address this, further analysis under the assumption that [redacted] have indicated that CZP escalation becomes the cost-effective treatment strategy across all analyses, reducing uncertainty over true treatment costs for increasing the dose from 200 mg to 400 mg of certolizumab pegol. [redacted], considering the clinical desire to have an option to escalate to CZP 400mg Q2W that was acknowledged both at the 1st Appraisal Committee meeting and in the ACD (Section 3.10). It is clear that consideration of [redacted] The requested revisions to the relevant ACD sections (Section 1.2 and 3.22) are presented below. **Suggested revisions, Section 1.2 (page 3)** • **Current statement:** "*Stop certolizumab pegol at 16 weeks if the psoriasis has not responded adequately. An adequate response is defined as:* o *a 75% reduction in the PASI score (PASI 75) from when treatment started or* o *a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started."* • **Requested revision:** "*Stop or consider escalating the dose of certolizumab pegol at 16 weeks if the psoriasis has not responded adequately. An adequate response is defined as:* o *a 75% reduction in the PASI score (PASI 75) from when treatment started or* o *a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started.* *Account for the possibility of dose escalation only if there is a commercial arrangement in place in addition to the agreed PAS. (See Section 3.21)."* **Section 3.21 (page 19)** UCB considers that the submitted evidence, including the new analyses, are relevant evidence for the discussions at the second Committee meeting and consideration in the decision making, and thus should be reflected in Section 3.21. Furthermore, the cost-	

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			effectiveness analyses of the CZP escalation strategy considered by the ERG and UCB clearly indicate that there remains uncertainty around the true treatment costs of increasing the dose from 200 mg to 400mg of certolizumab pegol and that commercial arrangements would have an impact on relative costs – a conclusion which should also be considered in the decision making and thus reflected in the ACD.	

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7	Company	UCB	**Section 1.5 (page 4):** The current recommendations state that "*The choice between certolizumab pegol or another biological treatment*….", inaccurately implying that several biologic options have been assessed during this appraisal, in addition to certolizumab pegol. UCB considers that there is potential for ambiguity and bias against the use of certolizumab pegol and this recommendation is built on statements used in multiple technology appraisals and not consistent with those from recent single technology appraisals in psoriasis. For instance, the recent NICE TA521 (guselkumab for treating moderate to severe plaque psoriasis) states "*If patients and their clinicians consider guselkumab to be one of a range of suitable treatments, including ixekizumab and secukinumab, the least costly (taking into account administration costs and commercial arrangements) should be chosen*." Furthermore there is ambiguity with respect to the basis upon which a treatment is considered "suitable" and UCB believe that greater emphasis should be placed upon the importance of clinical factors when patients and clinicians are selecting a treatment. Where multiple treatment options are "suitable", it may be that a particular treatment or treatments offer greater potential clinical value to patients, or are associated with unique benefits. The ACD states that the Appraisal Committee is interested in receiving comments on whether recommendations are a sound and suitable basis for guidance to the NHS. In this regard, UCB therefore requests that the Committee consider amending this recommendation so that it is consistent with previous guidance. **Suggested revisions, Section 1.5 (page 4)** • **Current statement:** "*The choice between certolizumab pegol or another biological treatment should be made after discussion between the patient and their healthcare professional about the advantages and disadvantages of the treatments available. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage, price per dose and commercial arrangements*." **Requested revision:** "*If patients and their clinicians consider certolizumab pegol to be one of a range of suitable biologic treatments, the clinical choice should be made after discussion about the advantages and disadvantages of the treatments available. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage, price per dose and commercial arrangements)."*	Comment noted. The text has been amended. Please see section 1.3 of the final appraisal document.
8	Company	UCB	**Section 1.1 (page 3)**	Comments noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			In Section 1.1 (page 3), the ACD states that "*Certolizumab pegol (200 mg) is recommended as an option for treating plaque psoriasis in adults.*" UCB asks that this statement is updated to remove reference to 200 mg specifically. As per the certolizumab pegol Summary of Product Characteristics, "*The recommended starting dose of Cimzia for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4.*"[11] Only after the loading dose (equivalent to 400 mg Q2W), is certolizumab pegol administered at a dose of 200 mg Q2W. Reference in Section 1.1 to 200 mg has the potential to cause confusion and advocate use of certolizumab pegol without loading dose, contrary to the approved summary of product characteristics.	The text has been amended where required to clarify that 200 mg refers to the maintenance dose.
			Section 1.1 also states that use of certolizumab pegol is subject to the condition that "*The company provides the drug according to the commercial arrangement.*" UCB asks that Section 1.1 is updated to refer to the Patient Access Scheme, instead of a commercial arrangement, in order to ensure alignment with UCB's company submission, and previous NICE recommendations for certolizumab pegol, for active psoriatic arthritis,[12] rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor,[13] rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed[14] and axial spondylarthritis.[15] **Suggested revisions, Section 1.1 (page 3)** • **Current statement:** *"Certolizumab pegol (200 mg) is recommended as an option for treating plaque psoriasis in adults, only if:…The company provides the drug according to the commercial arrangement"* **Requested revision:** *"<u>Certolizumab pegol is recommended</u> as an option for treating plaque psoriasis in adults, only if:…The company provides the drug according to the <u>Patient Access Scheme.</u>"*	The reference to the “commercial arrangement” reflects current NICE editorial standards. Patient access schemes are a type of commercial arrangement.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
9	Company	UCB	**Section 3.7 (page 10)** With regards to the Company's base-case network meta-analysis, Section 3.7 (page 10) of the ACD states that "*It showed that certolizumab pegol resulted in PASI 75 response rates that were:* • *Higher (but not statistically significantly so) than the biologicals with the same mechanism of action (that is, the TNF-alpha inhibitors, adalimumab and etanercept)* • *Statistically significantly higher than etanercept"* UCB believes that this statement could cause confusion with respect to the NMA results against etanercept. Since certolizumab pegol was associated with statistically significantly higher PASI75 response rates compared to etanercept according to the base-case network meta-analysis, UCB suggests that the mention of etanercept is removed from the first bullet point. The revisions requested by UCB are detailed below: **Suggested revisions, Section 3.7 (page 10)** • **Current statement:** *"It showed that certolizumab pegol resulted in PASI 75 response rates that were:* o *higher (but not statistically significantly so) than the biologicals with the same mechanism of action (that is, the TNF-alpha inhibitors, adalimumab and etanercept)* o *statistically significantly higher than etanercept"* • **Requested revision:** *"It showed that certolizumab pegol resulted in PASI 75 response rates that were:* o *higher (but not statistically significantly so) than the biologicals with the same mechanism of action (that is <u>the TNF-alpha inhibitor, adalimumab)</u>* o *statistically significantly higher than etanercept"*	Comment noted. The text has been amended. Please see section 3.11 of the final appraisal document.
10	Company	UCB	**Section 3.5 (page 9)** The ACD suggests in Section 3.5 (page 9) that "*none of the patients in the [certolizumab pegol] clinical trials had previously had phototherapy*". However, data presented in the company submission show that between one third and one half of patients in each of the	Comment noted. This statement refers to the subgroup of patients who are candidates for non-biological therapy and not the full

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
treatment arms in all three trials (CIMPASI-1, CIMPASI-2 and CIMPACT) had received prior chemophototherapy or phototherapy. According to data presented in the Form B appendices and in Table 12 below, the same is also true when the data for all three trials is pooled.

Table 9: Baseline characteristics for patients – Proportion of patients who had received prior chemotherapy or phototherapy (ITT population Pool E1)
<table>
<tr><th>Prior chemotherapy or phototherapy, n (%)</th><th>Placebo (n=157)</th><th>CZP 200 mg Q2W (n=351)</th><th>CZP 400 mg Q2W (n=342)</th></tr>
<tr><td>Yes</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>No</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Abbreviations: CZP: certolizumab pegol; Q2W: every two weeks.

Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1).

Source: UCB Cimzia Plaque Psoriasis Integrated Summary of Efficacy.[16]

UCB therefore requests that the incorrect statement is removed from the ACD, as suggested below.

Suggested revisions, Section 3.5 (page 9)

• Current statement: "The company stated that, in the CIMPASI and CIMPACT trials, similar PASI 75 response rates were reported in subgroups of patients who had previously had systemic treatment or phototherapy compared with those who had not. The committee noted that the subgroup of patients who had not had systemic non-biological treatment reflected the company's proposed positioning of certolizumab pegol at an earlier setting than that for biologicals in the NHS. The exception was that none of the patients in the clinical trials had previously had phototherapy."

Requested revision: "The company stated that, in the CIMPASI and CIMPACT trials, similar PASI 75 response rates were reported in subgroups of patients who had previously had systemic treatment or phototherapy compared with those who had not. The committee noted that the subgroup of patients who had not had systemic non-biological treatment reflected the company's proposed positioning of certolizumab pegol at an earlier setting than that for biologicals in the NHS. [Final sentence deleted.]"
</td><td>ITT population and is not an inaccuracy. The text has been amended for clarity. Please see section 3.7 of the final appraisal document.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
11	Clinical expert		Having looked at the recommendations on p3-4, there is no mention of use of the 400mg dose of certolizumab pegol. There is a proven benefit and clinical value with use of the 400mg dose in initial non or inadequate responders. In patients where the psoriasis has not initially responded to the 200mg dose, there is the opportunity to escalate to 400mg 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 400mg dose if there is an initial inadequate response, if the situation is cost-effective or there are local agreements in place. [Redacted] 4th Dec 2018	Comment noted. The committee considered the clinical and cost effectiveness evidence relating to dose escalation including new evidence submitted by the company Please see sections 3.12, 3.22 and 3.23 of the final appraisal document. The recommendations are unchanged. Please see sections 1.1 and 1.2 of the final appraisal document.
12	Professional group	British Association of Dermatologists	We would like to raise the point again that listing PUVA as a suitable treatment in the context of current treatment modalities is not appropriate and is frequently misinterpreted by CCGs as meaning clinicians have to justify or even use PUVA in their biologics pathway. This is bad practice and NICE are, by not changing this 'standard' wording, supporting this ongoing bad practice.	Comment noted. The wording of the recommendations has been amended to refer to "phototherapy." Please see sections 1.1 and 3.21 of the final appraisal document.
13	Patient group	Psoriasis and Psoriatic Arthritis Alliance	We welcome the positive recommendation of certolizumab pegol for treating chronic plaque psoriasis. People living psoriasis will be reassured that there will be further options and choice for them when other therapies begin to lose efficacy.	Comment noted.
14	Public	NHS professional	I understand that certolizumab has not currently been approved at 400mg. I just wanted to say as a dermatologist responsible for patients with severe psoriasis that frequently a higher dose than is identifed in clinical trials is needed in the hard to treat population. This has been recognised with several other biologics for psoriasis including ustekinumab and adalimumab which now allow doubling of the dose. Ability to vary the dose is very helpful in practice in the absence of any data showing an increase in adverse events.	Comment noted. The committee considered the clinical and cost effectiveness evidence relating to dose escalation including new evidence submitted by the company Please see sections 3.12, 3.22 and 3.23 of the final appraisal document. The recommendations are unchanged. Please see sections 1.1 and 1.2 of the final appraisal document.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
15	Public	NHS professional	s this recommendation pertains only to the CZP 200mg and it is mandated to stop if the response is not adequate it prohibits clinicians using the 400mg Q2W dose when we feel it is clinically needed. In current practice a subset of patients treated with biologics may have a sub-optimal response and might require dose escalation of therapy as a measure to improve efficacy. The phase III data for CZP in PSO shows a higher efficacy in the patients that are initiated on 400mg Q2W versus the 200mg Q2W and increasing efficacy in those patients that are escalated from 200mg Q2W to 400mg Q2W when their PASI response is below 75. Therefore, it would be beneficial to some patients if the use of the 400mg Q2W was allowed by amending the continuation criteria (section1.2) to allow dose escalation so that patients with a suboptimal response (PASI response of less than 75) could benefit from increased response to treatment. This 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. " "In my opinion the benefit of the escalation from 200mg Q2W to 400mg Q2W has not been fully represented in the ACD. As mentioned above the phase III data for CZP in PSO shows a higher efficacy in the patients that are initiated on 400mg Q2W versus the 200mg Q2W and increasing efficacy in those patients that are escalated from 200mg Q2W to 400mg Q2W when their PASI response is below 75. The data shows clear benefits in efficacy of increasing the dose of certolizumab pegol and it is important that this is accounted for in the interpretation of the evidence within the ACD and reflected in the recommendation. " "The recommendation states that Certolizumab and Adalimumab can be used for pregnancy and breastfeeding. It is great to have a number of choices of biologic that can be used in this patient group. However, it is important to acknowledge the significant differences in the structure of the antibodies, with Adalimumab retaining and Fc region compared to Certolizumab. The evidence is that Adalimumab crosses the placenta1, 2, and this may be of importance in its clinical use3.	Comment noted. The committee considered the clinical and cost effectiveness evidence relating to dose escalation including new evidence submitted by the company Please see sections 3.12, 3.22 and 3.23 of the final appraisal document. The recommendations are unchanged. Please see sections 1.1 and 1.2 of the final appraisal document. Please see section 3.25 of the FAD for the committee's conclusions on the use of certolizumab pegol during pregnancy and breastfeeding.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			1) Mahadevan et al. Clin Gastroenterol Hepatol. 2013 March ; 11(3): 286“e24. doi:10.1016/j.cgh.2012.11.011 2) Flint et al. Rheumatology, Volume 55, Issue 9, 1 September 2016, Pages 1693“1697 3) 3) Adalimumab SmPC. http://www(.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf.	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
16	Public	NHS professional	Certolizumab will provide a useful option in a number of patients most notably: 1. Pregnant females 2. Patients for whom a secondary non-response has been observed with adalimumab or other TNF inhibitor 3. Patients with a suboptimal response to other TNF inhibitors.	Comment noted.
17	Public	NHS professional	We welcome that the dose of 200mg is highlighted as the recommended dose in 1.1 esp as dose escalation to 400mg is mentioned in Chapter 2 as part of the SPC. Disease has not responded to ciclosporin, methotrexate and PUVA, or these options are contraindicated or not tolerated... This is in line with all other TAs but appears out of sync with feedback received from local clinicians who seem to consider UVB as an alternative. UVB is mentioned in the consultation document slides as part of the treatment pathway but not considered in the TA. Furthermore, the recommendation does not consider patients who are unable to attend PUVA due to work commitments whereas this is mentioned in the NICE CG. Lack of recommendations on sequential treatment and place in therapy. This will cause problems with providers as they invariably interpret that the drug should be available as an option for any patient fulfilling the criteria in section 1.1 (regardless whether this is 1st, 2nd, 3rd or even 4th line). We would appreciate a clear recommendation as to where in the biologic pathway the treatment sits.	Comment noted. The wording of the recommendations has been amended to refer to "phototherapy." Please see sections 1.1 and 3.21 of the final appraisal document. Providing recommendations on the optimum sequencing of biologics is beyond the scope of this guidance.
18	Commentator	LEO Pharma	We note that fourth line treatments Apremilast and Dimethyl fumarate were not considered as comparators for this appraisal. Bearing in mind the proposed positioning by the company for Certolizumab i.e as an alternative to: systemic non-biological treatments such as methotrexate, ciclosporin and acitretin, and following topical therapy and phototherapy; or biological treatments , the analysis seems incomplete without comparison versus Apremilast and Dimethyl Fumarate that are used as alternatives to biologics. Both these agents have been 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 technological appraisals (STAs) for Brodalumab included these treatments as comparators (Guselkumab was a fast track appraisal so did not require comparison to all available treatments) , thus the Certolizumab 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.	Comment noted. The rationale for the exclusion of apremilast and dimethyl fumarate has been added. Please see section 3.5 of the final appraisal document.
19	Commentator	LEO Pharma	The committee states on page 17 that *people with psoriasis, particularly those whose psoriasis does not respond to adalimumab, would value the option of an alternative TNF-alpha inhibitor that was more effective than etanercept and could be used during pregnancy.*	Comment noted. This sentence is intended to state that an anti-TNF which is more effective than etanercept would be valued and does

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			We are concerned that this may imply cycling through multiple anti-tnfs before moving onto other agents. Whilst PASI 75 is still being used as criteria to determine clinical effectiveness for biologics, with the more recent advances in newer classes of biological agents, PASI levels of 90 & 100 are now achievable for a greater number of patients compared to those seen with use of anti-tnfs. Having another anti-tnf like certolizumab , whilst providing choice especially during pregnancy, should not be used to delay use of more clinically effective treatments (that have also demonstrated cost-effectiveness), in the cohort of patients who may have already used an existing anti-tnf like adalimumab but not achieved adequate response.	not suggest a preferred treatment pathway (which is beyond the scope of this guidance).
20	Commentator	LEO Pharma	We agree with the proposal that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance.	Comment noted.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

January 2019

UCB Response to the ACD

File name	Version	Contains confidential information	Date
ID1232 ACD_UCB Response_FINAL 2019-01-04 [ACIC].docx		**Yes** AIC: Highlighted in yellow and underlined CIC: Highlighted in turquoise and underlined	**04-01-2019**

UCB welcomes the opportunity to respond to the Appraisal Consultation Document (ACD) on certolizumab pegol for treating chronic plaque psoriasis [ID1232].

UCB is pleased with the Appraisal Committee's preliminary recommendation of certolizumab pegol as a treatment option for adults with plaque psoriasis based on the criteria mentioned in Section 1.1 of the ACD.

Certolizumab pegol represents an important biologic treatment option for patients living with psoriasis and UCB welcomes the opportunity to be able to engage with NICE and NHS towards making certolizumab pegol available for patients and clinicians in England, Wales and Northern Ireland.

Following the review of the ACD, UCB would nevertheless like to raise a number of key points which should be considered at the second Appraisal Committee meeting, in particular related to:

- the consideration of all the evidence supporting the clinical benefits and the cost-effectiveness of increasing the dose of certolizumab pegol, and the reconsideration of the current ACD recommendation 1.2;
- the position of certolizumab pegol in the treatment pathway as an alternative treatment to current biologics;
- the differences in the molecular structure between biologics and the associated benefits.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**UCB Pharma Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**
Name of commentator person completing form:	**n/a**

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Section 3.10 (page 11)** *Clinical benefits of CZP 400 mg Q2W dose escalation in patients with insufficient response to CZP 200mg Q2W* ***Key point 1: Clinical benefits of the CZP dose escalation*** Section 3.10 (page 11) of the ACD states that "*When there is not a PASI 75 response to the 200 mg certolizumab pegol dose, there may be a response to an increased dose*". UCB considers that this statement does not represent an accurate and full interpretation of the strength and breadth of the relevant evidence presented by UCB. UCB's response to the ERG clarification questions included further evidence, from the CIMPACT study, on the clinical benefit of increasing the dose to 400 mg Q2W in patients that initially received CZP 200 mg Q2W and either were PASI 50–74 responders (partial responders) at Week 16 (Table 1), or did not reach a PASI75 response (inadequate responders) at Week 16 (Table 2). Among the CZP 200 mg Q2W partial responders (PASI 50–74) who escaped to CZP 400 mg Q2W (Table 1), with [redacted]% of patients achieving a PASI75 response rate and [redacted]% of patients achieving a PASI90 response rate at Week 32, ie within 16 weeks after dose escalation to 400mg Q2W. These response rates further increased by Week 48, to [redacted]% for PASI75, and [redacted]% for PASI90.[1] **Table 1: PASI responder rates at Week 32 and 48 in patients receiving CZP 200mg Q2W who at Week 16 achieved a PASI50 response, but not a PASI75 response (partial responders) and escaped to CZP 400 mg Q2W (CIMPACT study)** 	Responder rate, % (95% CI)	CZP 200 mg Q2W/Esc CZP 400 mg Q2W (n=[redacted])	
---	---	---
	Week 32	Week 48
PASI50	[redacted]	[redacted]
PASI75	[redacted]	[redacted]
PASI90	[redacted]	[redacted]
PASI100	[redacted]	[redacted] | Observed case. Source: Company's response to the ERG clarification Among CZP 200 mg Q2W patients who had an inadequate response (did not reach PASI75) at Week 16 and escaped to CZP 400 mg Q2W (Table 2), the majority ([redacted]%) achieved a PASI75 response at Week 32 (i.e. 16 weeks after dose escalation), and [redacted]%[i] of patients achieved a PASI90 response at Week 32. These responses further increased at Week 48 (i.e. 32 weeks after dose escalation) with [redacted]% of patients achieving a PASI75 response, and [redacted]% of patients achieving a PASI90 response.[2] Furthermore, among patients that achieve PASI 75 by Week 48 after escalating to CZP 400mg, [redacted]% had already reached a PASI90 response by Week 48. **Table 2: PASI responder rates at Week 32 and 48 in patients receiving CZP 200mg Q2W who failed to achieve PASI75 response at Week 16 and escaped to CZP 400 mg Q2W (CIMPACT study)** | Responder rate, % (95% CI)	CZP 200 mg Q2W/Esc CZP 400 mg Q2W (n=[redacted])	
---	---	---
	Week 32	Week 48
PASI50	[redacted]	[redacted]
PASI75	[redacted]	[redacted]
PASI90	[redacted]	[redacted]
PASI100	[redacted]	[redacted]	 Non-responder imputation Source: Company's response to the ERG clarification [i]Value corrected/updated vs Table 34 of the UCB response to the ERG clarification questions. These results demonstrate that [redacted] of patients who achieve only a partial response at week 16 with CZP 200 mg Q2W go on to achieve a PASI75 response 16 weeks later by escalating to the higher dose of 400 mg Q2W, and furthermore that this response increases at 32 weeks after dose escalation.

	The ACD states that the Appraisal Committee is interested in receiving comments on whether all relevant data has been taken into account and whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. Based on the evidence provided above, UCB consider that the conclusions in Section 3.10 of the ACD do not adequately account for all of the relevant evidence submitted and that the conclusions regarding clinical effectiveness of CZP dose escalation are not reflective of the evidence available for the clinical efficacy of CZP dose escalation and are therefore not reasonable interpretations. UCB therefore requests that the Committee reconsiders their interpretation, summary and conclusions regarding the clinical efficacy of CZP dose escalation and revises the ACD wording accordingly and consequently reconsider the recommendation in Section 1.2. Further details of UCB's requested revisions to Section 1.2, in light of the clinical evidence presented in this Comment and discussions of the cost-effectiveness of the CZP escalation strategy in Comment 2, are detailed in Comment 6. ***Key point 2: Alignment of the discussion of the evidence base for clinical efficacy and cost-effectiveness of CZP escalation*** The discussion of clinical efficacy of CZP escalation in Section 3.10 of the ACD determines that patients who do not achieve a PASI75 response to CZP 200 mg Q2W could benefit clinically from dose escalation. In Section 3.21 (page 18), the ACD states that "*the cost effectiveness of the strategy of increasing the dose of certolizumab pegol in people with a partial response (defined as PASI 50 to a PASI 75) should be considered*". UCB notes that there is misalignment between Section 3.10 and Section 3.21 in terms of the evidence base discussed for the clinical efficacy and cost-effectiveness of CZP dose escalation: there is no discussion in Section 3.10 of the clinical benefit of dose escalation in patients with partial response (PASI 50 to PASI 75), although this is the patient group in which the cost-effectiveness of the CZP dose escalation strategy is then considered in Section 3.21. Clinical evidence in support of dose escalation in partial responders was provided by UCB as part of the response to ERG clarification questions and was used to inform the economic analysis discussed in Section 3.21 (as noted in key point 1 above). UCB thus consider that the clinical efficacy data in these subgroups should also be noted in Section 3.10, to ensure clarity over the available clinical evidence and the evidence base used to inform the economic analysis of dose escalation of CZP. UCB requests that the Appraisal Committee considers the evidence outlined in Key Points 1 and 2, as relevant and a suitable basis for guidance to the NHS, and further requests that it is accurately reflected in the ACD. UCB provide the below suggested revisions that we consider appropriately reflect the clinical evidence for CZP dose escalation and ensure alignment between the discussions of the clinical efficacy (ACD Section 3.10) and cost-effectiveness (ACD Section 3.21) for CZP escalation. **Suggested revisions, Section 3.10 (page 11)** • ***Current statement:*** ***"****When there is not a PASI 75 response to the 200 mg certolizumab pegol dose, there may be a response to an increased dose…The company presented clinical evidence showing that, if there is not a PASI 75 response after 16 weeks of treatment with a dosage of certolizumab pegol 200 mg every 2 weeks, there may be a response if this is increased to 400 mg every 2 weeks."* • ***Requested revision:*** ***"****When there is not a PASI 75 response to the 200 mg certolizumab pegol dose, <u>there is an improved response</u> to an increased dose…The company presented clinical evidence showing that, if there is not a PASI 75 response<u>, or where there is a partial response (≥PASI 50 response but <PASI 75 response),</u> after 16 weeks of treatment with a dosage of certolizumab pegol 200 mg every 2 weeks, there <u>is</u> a <u>clinical</u> response if this is increased to 400 mg every 2 weeks."*
2	**Section 3.21, pages 18-19** <u>*Cost-effectiveness of the CZP escalation strategy*</u> Section 3.21 of the ACD presents the summary of the Committee's considerations regarding the economic analysis for CZP dose escalation (i.e. increasing the dose of CZP from 200mg Q2W to 400mg Q2W in patients with a partial response (defined as PASI 50 to a PASI 75) to CZP 200mg Q2W). The conclusion in the ACD is that the CZP dose escalation strategy is not cost-effective. Furthermore, as indicated in the ACD, the ERG considered that in addition to the comparison to alternative comparator dose escalation strategies, the CZP dose escalation strategy should have

been compared to strategy of switching to a next biological treatment. While UCB's submitted economic analysis and conclusion (CZP dose escalation being more effective and less costly than ADA escalation strategy) are briefly mentioned, the ACD indicates that the Committee conclusion is based on the sole consideration of the results of the ERG analysis, which is noted to have an ICER over £500,000 per QALY gained.

UCB considers that the Committee conclusion is not based on a full and thorough consideration of clinically relevant comparisons and all available evidence. In this context, and given the proven clinical benefits associated with the increase of the CZP dose to 400mg Q2W (as per the submitted evidence, re-emphasised in Comment 1 earlier in this response) and the clear clinical desire for the possibility to escalate CZP in clinical practice (as noted in Section 3.10 of the ACD), UCB considers that conclusions regarding the cost-effectiveness of CZP escalation should be based on a full appraisal of the various potential approaches and the resulting balance of evidence.

UCB would like to raise a number of points of concern which should be considered at the second Appraisal Committee meeting, summarized in Section 1 below. Firstly, UCB would like to highlight an apparent error in the ACD reporting of the analysis on which the Committee decision appears to be based (i.e. the analysis producing an ICER >£500,000 per QALY gained). Secondly. UCB highlight a key concern with the exclusion from consideration of clinically relevant comparisons of the CZP dose escalation strategy, which results in a Committee decision that is based on a single analysis and not full consideration of the health economic evidence. Finally, UCB raise a consideration regarding a potential source of bias in the analysis on which the Committee decision has been based. These concerns are presented in more detail in Section 1 below.

Based on these concerns, UCB provide an overview of ICERs from a range of additional cost-effectiveness analyses evaluating CZP dose escalation, taking on board previous ERG and NICE Committee comments as to preferred modelling approaches (Section 2 below). From these analyses it is clear that the choice of the comparator for the CZP dose escalation has a notable effect on the estimated true relative treatment costs associated with CZP dose escalation and hence the conclusions regarding cost-effectiveness. Nevertheless, the conclusions of these new scenario analyses support the cost-effectiveness of the CZP dose escalation with the current PAS. Furthermore, it is also clear that consideration of [redacted] As such, on the balance of the available evidence it is reasonable to conclude that CZP dose escalation can provide a cost-effective treatment option to the NHS for the treatment of adults with moderate to severe plaque psoriasis. Consequently, UCB considers that this new evidence is relevant for consideration at the second Appraisal Committee meeting to inform the Committee recommendations with respect to the potential use of the CZP dose escalation (ACD recommendation 1.2).

1. <u>Points of concern with the analysis on which the Committee preliminary decision regarding CZP dose escalation</u>

Incorrect reporting of the ICER for CZP dose escalation in the ACD

The ERG analysis producing an ICER over £500,000 per QALY gained is stated in the ACD to be based on comparison of the following sequences (Section 3.21, page 18):

- *CZP 200mg→CZP 400mg→UST 90mg→IFX→BSC*
- *CZP 200mg→UST 90mg→IFX→BSC*

UCB believe this is incorrect. Following the review of the ERG version of the UCB submitted model, running the above sequence results in an ICER of £122,560.18. The only ICER relating to the dose escalation analysis that is >£500,000 per QALY gained, mentioned in the ERG report addendum (£533,154 per QALY gained), is based on the following sequences:

- *CZP 200mg→CZP 400mg→BSC→BSC→BSC*
- *CZP 200mg→UST 90mg→BSC→BSC→BSC*

UCB therefore believes that the ACD should be revised to accurately reflect the sequences considered by the ERG in relation to this ICER.

Regardless of this error in reporting, UCB acknowledge that the ICER resulting from either sequence is above conventional NICE cost-effectiveness thresholds. However, UCB consider that drawing conclusions from this single ICER as it is reported in the ACD does not constitute a full and thorough consideration of clinically relevant comparisons and all available evidence.

Decision based on a single analysis and not full consideration of the health economic evidence

UCB maintain that the relevant comparison to a strategy of CZP dose escalation is to an alternative escalation strategy of ADA. This is because the CZP escalation strategy considers the case where an escalation strategy to a higher dose of the existing treatment is considered the most appropriate clinical course of action if possible. The most relevant comparison is therefore to the currently available treatment option for clinicians wishing to follow a treatment strategy of maintenance on the existing therapy through escalation (rather than having to undergo a switch to a different treatment option, which may be felt to be clinically less appropriate, particularly in the case where patients have obtained partial response to their initial treatment). The appropriate comparison is therefore a comparison to ADA escalation, which is licensed for a dose increase in the case of inadequate response. As such, UCB wish to re-iterate the relevance of the revised base case analysis submitted in the proforma response to the ERG report (UCB proforma response appendices, Table 6), which represent the latest base case.

UCB acknowledge that the ACD states that. "…*in addition to being compared with a different dose escalation strategy, the dose escalation sequence should also be compared with switching to the next biological treatment in the treatment pathway*" (ACD, Section 3.21). However, when considering switch strategies as comparators the ACD currently fails to acknowledge that a switch to UST 90mg is not the only switch that might be considered clinically appropriate. Guselkumab and brodalumab are relatively recently approved for use in the NHS and do not currently represent the standard clinical practice for a second-line therapy; however, it is very plausible in practice that a clinician may consider secukinumab or ixekizumab, as alternative options to UST 90mg, as second-line therapy switch therapy in patients for whom CZP does not provide a sufficient response.

Therefore, UCB consider that any evaluation of CZP dose escalation versus a switch strategy should consider the results of economic analyses across other potentially relevant switch strategies, and not be based solely on the single comparison to a switch to UST 90mg.

Source of bias in the single analysis considered by the Committee

In the ERG's analysis, the efficacy data over the first two lines of therapy (i.e. CZP 200mg→CZP 400mg, or CZP 200mg→UST 90mg) is modelled by the ERG as follows:

Table 3: Efficacy sources for modelling 1st line and 2nd line in the ERG's dose escalation analysis presented in the ACD (ICER >£500,000 per QALY gained)

	CZP dose escalation strategy *(CZP 200mg > CZP 400mg > BSC > BSC > BSC)*	**"Switch" to UST 90mg strategy** *(CZP 200mg > UST90 > BSC > BSC > BSC)*
1st line	CZP 200mg efficacy based on results of NMA	CZP 200mg efficacy based on results of NMA
2nd line	CZP 400mg efficacy based on weighted average of: • *For the proportion of patients considered to be partial responders (PASI 50-74) to CZP 200mg:* clinical data provided by UCB for efficacy of CZP 400mg in the population of partial responders (PASI 50-74) to CZP 200mg from the CIMPACT study • *For the proportion of patients considered to be non-responders (PASI <50) to CZP 200mg:* UST 90mg efficacy based on results of NMA, in order to model that non-responders to CZP 200mg would switch to UST 90mg rather than escalate	UST 90mg efficacy based on results of NMA

Source: Section 5.2 (ERG report)/Section 5.2 (ERG Report Addendum) describe the sequences compared. Efficacy sources determined through review of the ERG model.

Considering each treatment arm in isolation, the above choices of efficacy sources initially appear reasonable. For CZP dose escalation, clinical data for efficacy of CZP 400mg as escalation is available and it is therefore logical to utilise this. For the switch to UST90mg, it is assumed that the NMA-derived efficacy holds for the use of UST 90mg as a second-line therapy. This implicitly assumes that UST 90mg has the same efficacy when used as a 1st line treatment as when used

at 2nd line. This potentially inflates the efficacy of UST 90mg in the 2nd-line, as it would be expected that efficacy of biologics would decrease with each line of therapy. Such an assumption – whereby an NMA used to inform 1st-line efficacy is used to model 2nd and later-line efficacy – is common practice in the absence of any more appropriate data, and commonly the bias resulting from this potential efficacy inflation is limited in nature because the same assumption applies in all model arms. However, in the analysis of the ERG described above this inflated efficacy does not apply equally to both arms, because in the CZP escalation arm it is data from the CIMPACT study and not from the NMA that is used to model treatment efficacy of CZP 400mg as a 2nd-line treatment in patients who have responded only partially to CZP 200mg. As such, the approach to modelling efficacy that is outlined in Table 3 introduces a bias, and this bias is not acknowledged by the ERG or the Committee in the ACD. The impact of this bias can be explored by using the same efficacy source in both treatment arms.

Summary of concerns

In summary, UCB consider that it is inappropriate to base decisions regarding the cost-effectiveness of CZP dose escalation on a single analysis comparing a CZP escalation strategy to a "switch" to UST 90mg strategy as it is currently reflected in the ACD. The most appropriate comparison is to a dose escalation strategy of ADA 40mg to ADA 80mg. Acknowledging that the ERG take a differing view and consider comparisons to a switch strategy to be more appropriate, the decision should be based on balanced consideration across the range of potentially relevant comparisons, including both comparisons to an ADA escalation strategy and comparisons to switch strategies. In addition, the impact of the source of bias in the ERG's current analysis should be considered for decision-making.

2. **<u>New analyses supporting the cost-effectiveness of CZP dose escalation</u>**

Given the above, UCB present results from a number of new scenario analyses supporting the cost-effectiveness of the CZP dose escalation strategy that are relevant to be considered by the Appraisal Committee at the second meeting. In doing so, UCB have taken into account previous considerations of the ERG and the Committee, as outlined in Section 3.18 of the ACD, that "…*treatment sequences, although more likely to reflect the treatment switching seen in clinical practice, may have provided misleading cost-effectiveness estimates for certolizumab pegol*". The ACD notes that to address these issues the ERG performed analyses setting subsequent options in sequences to best supportive care. Therefore, UCB has provided analyses both with treatment sequencing and removing treatment sequencing (i.e. all subsequent treatment options set to BSC after the escalated therapy/switch biologic) in order to assess the influence of treatment sequencing on results.

The analyses for which results are provided are outlined in Table 4 below. Firstly, UCB maintain that the comparison to ADA escalation is the appropriate comparison and therefore re-iterate the revised base case from the UCB proforma response to the ERG report, which represents the latest base case. Subsequently, the concerns raised in Section 1 above are addressed through the presentation of additional analyses that:

- consider additional comparisons to other switch strategies (SEC, IXE)

  and

- explore the impact of the potential source of bias by aligning efficacy sources between the CZP escalation and comparator arms. Two conservative approaches are explored, which in both cases consider the separate populations of partial responders (PASI50-74) and non-responders (PASI<50) to initial therapy and align the sources of efficacy for these populations as appropriate between the CZP escalation and comparator arms:

  1. For partial responders: the efficacy estimates of the 2nd line biologic treatment comparator is assumed to be the same as the clinical efficacy data of CZP 400mg in the population of partial responders (PASI 50-74) from the CIMPACT study

  2. For non-responders: the efficacy estimate for both the CZP 400mg and the comparator is assumed to be based on the respective NMA estimates for the therapy received by partial and non-responders

     A detailed description of the approach to efficacy alignment is provided in Appendix 1 to this response.

With the exception of the above adjustments for efficacy sources and the sequences modelled, the new scenario analyses presented in this response are based on the same model and assumptions considered for the UCB latest base case cost-effectiveness results for the CZP escalation strategy, included in the pro forma response to the ERG report (UCB proforma response, Table 6). A summary of the sequences modelled for the new scenario analyses below versus the approach in the UCB latest basecase (response proforma) and the ERG's approach that gave rise to the ICER quoted in the ACD is provided in Appendix 2.

Table 4: Summary of presented analyses

Analysis	Notes
Base case analysis	
UCB proforma response analysis (CZP escalation vs ADA escalation – sequences)	The updated base case analysis for the PASI 50-74 response at Week 16 group, provided in Table 6 of the UCB proforma response appendix.
Additional scenario analyses	
1. CZP escalation vs ADA escalation – sequences	This analysis is the same as the base case analysis but explores the efficacy adjustment described above
2. CZP escalation vs ADA escalation – no sequences	This analysis is the same as the base case analysis but explores the efficacy adjustment described above and removes treatment sequencing
3. CZP escalation vs switch to SEC – sequences	New analysis that explores the efficacy adjustment described above and considers the comparison to a switch to SEC strategy
4. CZP escalation vs switch to IXE – sequences	New analysis that explores the efficacy adjustment described above and considers the comparison to a switch to IXE strategy
5. CZP escalation vs switch to SEC – no sequences	As above switch to SEC analysis, but removing treatment sequencing
6. CZP escalation vs switch to IXE – no sequences	As above switch to IXE analysis, but removing treatment sequencing
7. CZP escalation vs switch to UST – no sequences	This analysis is the same as the switch to SEC and switch to IXE analyses above but models a switch to UST 90mg instead, similarly to the latest ERG analysis quoted in the ACD. This analysis is the same as the ERG analysis that gives rise to the ICER >£500k (quoted in the ACD) but explores the impact of the efficacy adjustment.

It should be noted that all analyses of CZP dose escalation presented to date may inflate the costs associated with CZP 400mg, and this remains a limitation of the revised analyses presented below. To model the CZP escalation sequence, CZP 400mg Q2W is modelled as the second-line treatment in the sequence in order to fit with the model structure. This means that all patients who are initially responders to 1st line CZP 200mg Q2W, who continue to maintenance CZP 200mg and who then discontinue maintenance therapy currently move to receive escalated CZP 400mg in the model. This discontinuation of CZP 200mg Q2W maintenance therapy is based on the 20% annual withdrawal rate assumption for the maintenance period of biologics and captures discontinuation both due to loss of efficacy and due to adverse events. While patients who withdraw from CZP 200mg maintenance due to loss of efficacy may well be considered for dose escalation, patients who withdraw due to adverse events on CZP 200mg would not be escalated in clinical practice to CZP 400mg. These patients would likely instead move to a different biologic. However, the model structure currently does not allow this: patients who discontinue from their 1st line maintenance therapy must move to the 2nd line therapy in the sequence (which is CZP 400mg Q2W in the CZP escalation arm). As such, the model currently inflates the use of CZP 400mg by the proportion of patients who would discontinue maintenance CZP 200mg due to adverse events. The same limitation applies to comparator escalation sequences (i.e. costs of ADA escalation are similarly inflated due to the same model limitation) and so this is not a relevant concern for the comparison to alternative escalation strategies. However, because there is no inflation of costs in the comparator arm for the comparisons to switch strategies (it is accurate to assume that patients discontinuing maintenance CZP 200mg due to both loss of efficacy and adverse events would switch to a new biologic), this limitation means that the ICERs presented below for CZP escalation versus the switch strategies may be conservative.

The results of the set of analyses that UCB believe should be considered in full to inform decision-making are presented below in Table 5 (re-iteration of the UCB base case analysis) and Table 6 (results of new scenario analyses, including comparisons to alternative switch strategies and exploration of efficacy adjustments). Full tables of results (detailing total and incremental costs and QALYs in addition to ICERs) are provided in Appendix 3 to this response.

The analyses conducted provide results across a broad range of possible comparisons and indicate the following:

- CZP dose escalation is cost-effective in 11/15 analyses, with the only exceptions being the comparison to ADA escalation without sequencing and the comparison to a switch to UST strategy, highlighting that the ERG ICER quoted in the ACD is not representative of the full spectrum of plausible cost-effectiveness results for CZP escalation.

- The analysis conducted by the ERG and referenced in the Committee decision-making in the ACD (i.e. the comparison to switch to UST 90mg) represents the most pessimistic ICER amongst 15 clinically plausible comparisons and therefore does not reflect a balanced consideration of the evidence.

- Results are generally robust to the exploration of alternative efficacy assumptions. Whilst each of the two assumptions explored is associated with inherent limitations regarding the validity of the necessary assumptions, this should provide confidence that the results of the analyses are generally robust to exploration of the source of bias in the efficacy assumptions that is described above. Of interest, when addressing the source of bias in the efficacy assumption by using the NMA efficacy in both treatment arms, the ICER for the comparison to the switch to UST 90mg (the equivalent of the ERG ICER quoted in the ACD) drops considerably.

- In the majority of analyses, differences in incremental QALYs are small, indicating relative stability of the estimates of incremental benefit of the CZP dose escalation. This highlights that the uncertainty relates primarily to the estimation of the incremental costs associated with CZP escalation. It should also be noted that the high ICER in the comparison to the switch to UST 90 is a product of small incremental QALYs.

Consideration of the cost-effectiveness results across the range of potentially relevant comparisons presents a considerably different case for the cost-effectiveness of CZP escalation compared to that presented in the ACD, which is based on consideration of a single ICER. Consequently, UCB believe that the results included in this response should be considered in the second Appraisal Committee meeting and the Committee decision, to ensure all relevant evidence has been accounted for.

UCB acknowledge that when considering the range of analyses presented below supporting the cost-effectiveness of the CZP dose escalation, uncertainty still remains regarding the true incremental costs of increasing the dose of CZP. Therefore, results where [redacted] are presented in Table 7 (re-iteration of the UCB latest base case analysis) and Table 8 (results of new scenario analyses, including comparisons to alternative switch strategies and exploration of efficacy adjustments). Full detailed results are provided in Appendix 4. Under this assumption, CZP escalation becomes the cost-effective treatment strategy across all analyses, reducing uncertainty over true treatment costs for increasing the dose from 200 mg to 400mg of certolizumab pegol. [redacted], considering the clinical desire to have an option to escalate to CZP 400mg Q2W that was acknowledged both at the 1st Appraisal Committee meeting and in the ACD (Section 3.10). It is important to note that in a previous appraisal considering dose escalation for infliximab and adalimumab in the context of Crohn's disease (NICE TA187), it was ultimately noted that *"the Committee remained uncertain about true treatment costs for infliximab and adalimumab and accepted that local arrangements would have an impact on relative costs"*. The analyses presented in this response reflect a similar situation where there is clear clinical desire for dose escalation and uncertainty around true treatment costs depending on the specific analysis considered to assess the cost-effectiveness of the dose escalation. The additional analyses accounting for [redacted] clearly indicate that CZP is a cost-effective treatment option across all analyses considered [redacted] further supporting the conclusions of the cost-effectiveness analyses of the CZP dose escalation with the agreed PAS. On this basis, UCB would consider that similar wording would be appropriate for the case of dose escalation from CZP 200mg to CZP 400mg in Section 3.21 of the ACD.

Table 5: Latest base case cost-effectiveness results for CZP escalation strategy (CZP with PAS)

First-line therapy	Subsequent sequence	Total		Incremental		ICER
		QALYs	Costs	QALYs	Costs	
Efficacy assumptions for CZP (PASI 50-74 response at week 16)						
CZP 200mg	CZP400mg, UST, IFX, BSC	[redacted]	[redacted]			
ADA 40mg	ADA80mg, UST, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	CZP dominates

Source: Table 6, Appendix of UCB Pro Forma Response to ERG report.

Table 6: New cost-effectiveness scenario analyses for CZP escalation strategy (CZP with PAS)

Comparison	First-line therapy	Subsequent sequence	ICER Aligning to CZP 400mg CIMPACT partial responders efficacy	ICER Aligning to NMA efficacy
Comparison to ADA escalation				
Modelling sequences of treatments				
CZP escalation	CZP 200mg	CZP 400mg, UST 90mg, IFX, BSC	-	-
vs ADA escalation	ADA 40mg	ADA 80mg, UST 90mg, IFX, BSC	£22,370	£28,354
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)				
CZP escalation	CZP 200mg	CZP 400mg, BSC, BSC, BSC	-	-
vs ADA escalation	ADA 40mg	ADA 80mg, BSC, BSC, BSC	£35,481	£39,489
Comparison to switch strategies				
Modelling sequences of treatments				
CZP escalation	CZP 200mg	CZP 400mg, UST 90mg, IFX, BSC	-	-
Switch to SEC	CZP 200mg	SEC, UST 90mg, IFX, BSC	£147,965 (SW*)	£134,435 (SW*)
Switch to IXE	CZP 200mg	IXE, UST 90mg, IFX, BSC	£200,461 (SW*)	£132,245 (SW*)
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)				
CZP escalation	CZP 200mg	CZP 400mg, BSC, BSC, BSC	-	-
Switch to SEC	CZP 200mg	SEC, BSC, BSC, BSC	£148,126 (SW*)	£133,868 (SW*)
Switch to IXE	CZP 200mg	IXE, BSC, BSC, BSC	£201,308 (SW*)	£130,462 (SW*)
Switch to UST 90mg	CZP 200mg	UST90, BSC, BSC, BSC	£523,460	£313,525

*SW indicates a south-west ICER (i.e. CZP escalation strategy associated with lower QALYs and lower costs. These ICERs have been presented as the ICER for the comparator sequence versus the CZP escalation sequence for ease of interpretation. Therefore, SW ICERs above £30,000 indicate that the CZP escalation strategy is cost-effective at conventional thresholds.

Table 7: Latest base case cost-effectiveness results for CZP escalation strategy ([redacted])

		Total	Incremental	ICER

First-line therapy	Subsequent sequence	QALYs	Costs	QALYs	Costs	
CZP 200mg	CZP 400mg, UST, IFX, BSC	[redacted]	[redacted]			
ADA 40mg	ADA 80mg, UST, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	CZP dominates

Source: Table 6, Appendix of UCB Pro Forma Response to ERG report.

Table 8: New cost-effectiveness scenario analyses for CZP escalation strategy ([redacted])

Comparison	First-line therapy	Subsequent sequence	ICER Aligning to CZP 400mg CIMPACT partial responders efficacy	ICER Aligning to NMA efficacy
Comparison to ADA escalation				
Modelling sequences of treatments				
CZP escalation	CZP 200mg	CZP 400mg, UST 90mg, IFX, BSC	-	-
vs ADA escalation	ADA 40mg	ADA 80mg, UST 90mg, IFX, BSC	CZP dominates	CZP dominates
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)				
CZP escalation	CZP 200mg	CZP 400mg, BSC, BSC, BSC	-	-
vs ADA escalation	ADA 40mg	ADA 80mg, BSC, BSC, BSC	CZP dominates	CZP dominates
Comparison to switch strategies				
Modelling sequences of treatments				
CZP escalation	CZP 200mg	CZP 400mg, UST 90mg, IFX, BSC	-	-
Switch to SEC	CZP 200mg	SEC, UST 90mg, IFX, BSC	£944,479 (SW*)	£857,370 (SW*)
Switch to IXE	CZP 200mg	IXE, UST 90mg, IFX, BSC	£884,443 (SW*)	£521,948 (SW*)
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)				
CZP escalation	CZP 200mg	CZP 400mg, BSC, BSC, BSC	-	-
Switch to SEC	CZP 200mg	SEC, BSC, BSC, BSC	£948,659 (SW*)	£844,154 (SW*)
Switch to IXE	CZP 200mg	IXE, BSC, BSC, BSC	£891,737 (SW*)	£495,350 (SW*)
Switch to UST 90mg	CZP 200mg	UST90, BSC, BSC, BSC	£19,229	£23,760

*SW indicates a south-west ICER (i.e. CZP escalation strategy associated with lower QALYs and lower costs. These ICERs have been presented as the ICER for the comparator sequence versus the CZP escalation sequence for ease of interpretation. Therefore, SW ICERs above £30,000 indicate that the CZP escalation strategy is cost-effective at conventional thresholds.

3

Section 3.20 (page 17):

Within Section 3.20 (page 17), the Committee states that *"…people with psoriasis, particularly those whose psoriasis does not respond to adalimumab, would value the option of an alternative TNF-alpha inhibitor."*

UCB would like to note that the key clinical data and economic analysis for certolizumab pegol provided in the Company Submission related to the population of patients who were inadequate responders to systemic non-biologic therapy or candidates for systemic non-biologic, as per the marketing authorisation and the final NICE scope. Furthermore, for the inadequate responders to systemic non-biologic therapy population, the evidence included in the Company Submission was supportive of the requested positioning for CZP in the treatment pathway, in line with recommendation of other biologics for the treatment of moderate to severe plaque psoriasis, as a first-line biologic treatment option, which was agreed by the Committee, as noted in Section 3.3 of the ACD. UCB would like to note that the wording in Section 3.20 of the ACD does not accurately reflect the evidence submitted and considered by the Appraisal Committee for the appraisal of CZP in terms of the appropriate positioning of CZP. UCB considers that the statement in the ACD is not a reasonable interpretation of the evidence and the committee discussions, and therefore requests the removal of this wording from the ACD as per the suggested revised wording below.

	Suggested revisions, Section 3.20 (page 17) • **Current statement: "***The committee agreed that people with psoriasis, particularly those whose psoriasis does not respond to adalimumab, would value the option of an alternative TNF-alpha inhibitor that was more effective than etanercept and…"* • **Requested revision: "***The committee agreed that people with psoriasis would value the option of an alternative TNF-alpha inhibitor that was more effective than etanercept and…"*
4	**Section 3.11 (page 11, 12).** *Certolizumab pegol molecular structure and difference between biologics* ***Key point 1: Existence of relevant clinical data*** In Section 3.11 (page 11, 12) of the ACD, the Appraisal Committee highlights that, in light of the structure of certolizumab pegol (CZP), this drug "*would not be anticipated to cross the placenta*". While this statement is valid, UCB would like to note that this hypothetical phrasing is not commensurate with the existence of data from the CRIB pharmacokinetic study of 16 pregnant women receiving CZP 200 mg every two weeks (Q2W) or CZP 400 mg every four weeks (Q4W), which provides clinical evidence that there is no to minimal placental transfer of CZP from mothers to infants.[5] The Summary of Product Characteristics for CZP reflects the findings of the CRIB study by referencing that there is "low or negligible placental transfer". UCB therefore requests that Section 3.11 is updated to better reflect the availability of these clinical data and the extent to which the behaviour of CZP with regards to placental transfer is known and underpinned by evidence, including a statement on the conclusions of the evidence from CRIB and CRADLE. ***Key point 2: Differences between the anti-TNFs*** In Section 3.11 of the ACD, it is highlighted that "*The clinical experts stated that these data were consistent with the structure of certolizumab pegol, which would not be anticipated to cross the placenta. They considered certolizumab pegol could be used in pregnancy if needed and while breastfeeding. The only other biological treatment with a summary of product characteristics stating that it can be used in pregnancy and breastfeeding is adalimumab, while infliximab's summary of product characteristics states that it can be used during in breastfeeding*". UCB considers that the current summary of the evidence could be confusing and misleading, and requests certain revisions to this section to ensure a full context is provided of the existing evidence. Considering the conclusions of the clinical experts regarding the molecular structure of certolizumab pegol, the use of the wording "*The only other biological treatment*…" in the context of the preceding discussion suggests a resemblance or similarity between CZP and adalimumab, which could be incorrectly interpreted as suggesting that the structural elements of the CZP molecule that result in no to minimal placental transfer are shared by adalimumab. This is not the case: active transport of immunoglobulin G (IgG) across the placenta (occurring predominantly during the second and third trimesters of pregnancy)[5] is mediated by the neonatal fragment crystallisable (Fc) receptor (FcRn).[6] CZP has a unique molecular structure amongst biologics in lacking this Fc region, meaning it does not bind FcRn.[5, 7] While certolizumab pegol, adalimumab and infliximab are anti-TNFs, they do not share the same molecular structure, which is a critical element with respect to the active transport of immunoglobulin G (IgG). Furthermore, the current wording in the above statements from Section 3.11 may be incorrectly interpreted as suggesting that adalimumab and infliximab are not anticipated to undergo maternal to fetal placental transfer, given the current flow of Section 3.11 and the way that reference to these products follows on directly from the discussion of no to minimal CZP placental transfer and the linking of this to use of CZP in pregnancy and breastfeeding. However, in a study of pregnant women with Crohn's disease receiving anti-TNF treatment, the median ratio of cord to maternal drug level on the day of birth was 160% for infliximab, and 179% for ADA. In contrast, the median ratio of cord to maternal CZP level was 3.9%.[8] UCB would also like to note that the latest European Summary of Product Characteristics for both adalimumab (Humira®) and infliximab (Remicade®) report that these anti-TNFs may (adalimumab) or do (infliximab) cross the placenta, as indicated below: • "*Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy*."[9]

	• *"Infliximab crosses the placenta and has been detected in the serum of infants up to 6 months following birth."*[10] The latest Summary of Product Characteristics for certolizumab pegol states that "*Non-clinical studies suggest low or negligible level of placental transfer of a homologue Fab-fragment of certolizumab pegol (no Fc region)".* Other differences in Summary of Product Characteristics wording exist for CZP compared to adalimumab and infliximab in relation to women of childbearing potential and breastfeeding. Finally, according to the ACD, "*infliximab's summary of product characteristics states that it can be used during in breastfeeding*". However, UCB would like to highlight that infliximab's summary of product characteristics in fact states that "Infliximab should only be used during pregnancy if clearly needed", and that *"women must not breast feed for at least 6 months after Remicade treatment"*.[10] UCB thus considers it important that the ACD accurately reflects the difference between the molecules and the link between the molecular structure and use in women of childbearing potential, as well as pregnant and breastfeeding women, to ensure there is no risk of ambiguity by implying that these biologics are associated with identical considerations for these patients. UCB therefore requests that Section 3.11 is revised to make clear that the structure of CZP and the resulting impact on placental transfer from mothers to infants[5] are unique to CZP and that this section is reworded to avoid any ambiguity or potential for confusion in relation to any Summary of Product Characteristics, specifically any supporting or underlying evidence, data or findings around pregnancy and breastfeeding. UCB's suggested revisions to Section 3.11 of the ACD, addressing the above key points 1 and 2 are listed below (text underlined): **Suggested revisions, Section 3.11 (page 11, 12):** • **Current statement:** *"The summary of product characteristics for certolizumab pegol states that it can be used during pregnancy and breastfeeding. The evidence for this was based on 2 clinical studies (CRIB and CRADLE) and safety registry data collected on certolizumab pegol across its licensed indications. The clinical experts stated that these data were consistent with the structure of certolizumab pegol, which would not be anticipated to cross the placenta. They considered certolizumab pegol could be used in pregnancy if needed and while breastfeeding. The only other biological treatment with a summary of product characteristics stating that it can be used in pregnancy and breastfeeding is adalimumab, while infliximab's summary of product characteristics states that it can be used during in breastfeeding. The patient experts explained that people who are pregnant or who are considering pregnancy would welcome further effective treatment options for plaque psoriasis that do not need to be stopped before and during pregnancy, or while breastfeeding."* • **Requested revision:** *"The summary of product characteristics for certolizumab pegol states that it can be used during pregnancy and breastfeeding. The evidence for this was based on 2 clinical studies (CRIB and CRADLE) and safety registry data collected on certolizumab pegol across its licensed indications. <u>The CRIB study demonstrated no to minimal maternal-to-fetal placental transfer of CZP, while the CRADLE study demonstrated minimal transfer of CZP into breast milk.</u> The clinical experts stated that these data were consistent with the structure of certolizumab pegol <u>(Fc-free),</u> which would not be anticipated to cross the placenta. They considered certolizumab pegol could be used in pregnancy if needed and while breastfeeding. The only other biological treatment with a summary of product characteristics stating that it can be used in pregnancy and breastfeeding is adalimumab, while infliximab's summary of product characteristics states that it can be used during <u>pregnancy only if clearly needed, and that women should not breastfeed for up to 6 months after treatment</u>. <u>However, the summary of product characteristics for adalimumab and infliximab indicate that these may or do cross the placenta.</u> The patient experts explained that people who are pregnant, considering pregnancy <u>or breastfeeding</u> would welcome <u>an</u> effective treatment <u>option</u> for plaque psoriasis that do<u>es</u> not need to be stopped before and during pregnancy, or while breastfeeding."*
5	**Section 3.24 (page 21)** In Section 3.11, the Appraisal Committee reports that "*The patient experts explained that people…would welcome further effective treatment options for plaque psoriasis that do not need*

	to be stopped before and during pregnancy, or while breastfeeding." However, in Section 3.24 (page 21), it is noted that "*The committee understood that people would welcome an additional treatment option that can be used during pregnancy and the pre-conception period*." UCB considers that the section on Equality issues should be aligned with section 3.11 and also indicate the need for a treatment that can be used during breastfeeding (acknowledged by the Appraisal Committee in Section 3.11). UCB would thus request that Section 3.24 and Section 3.11 of the ACD are aligned to fully reflect the holistic needs among women of child-bearing age with psoriasis, i.e. a treatment option that can be used during the pre-conception period, during pregnancy, *and* while breastfeeding. **Suggested revisions, Section 3.24 (page 21):** • **Current statement: "***The committee understood that people would welcome an additional treatment option that can be used during pregnancy and the pre-conception period."* • **Requested revision:** "*The committee understood that people would welcome a treatment option that can be used during pregnancy (if clinically needed), the pre-conception period, and breastfeeding."*
6	**Section 1.2 (page 3)** In light of the previous comments and evidence presented by UCB in this document in relation to dose escalation for certolizumab pegol from both a clinical and cost-effectiveness standpoint, UCB asks that the ACD reconsiders the recommendations in Section 1.2 (page 3), as well as the supporting rationale provided in Section 3.22 (page 19). Specifically, as detailed in Comment 1, data from the CIMPACT study show that, when there is not a PASI75 response to certolizumab pegol 200 mg, there is an improved response to certolizumab pegol 400 mg: [redacted]% of patients who achieve only a partial response at week 16 with CZP 200 mg Q2W go on to achieve a PASI75 response 16 weeks later by escalating to the higher dose of 400 mg Q2W. Furthermore, this response increases at 32 weeks after dose escalation. UCB acknowledge that when considering the range of analyses presented as part of Comment 2, supporting the cost-effectiveness of the CZP dose escalation strategy, uncertainty might remain regarding the true incremental costs of CZP escalation. To address this, further analysis under the assumption that [redacted] have indicated that CZP escalation becomes the cost-effective treatment strategy across all analyses, reducing uncertainty over true treatment costs for increasing the dose from 200 mg to 400 mg of certolizumab pegol. [redacted], considering the clinical desire to have an option to escalate to CZP 400mg Q2W that was acknowledged both at the 1st Appraisal Committee meeting and in the ACD (Section 3.10). It is clear that consideration of [redacted]. The requested revisions to the relevant ACD sections (Section 1.2 and 3.22) are presented below. **Suggested revisions, Section 1.2 (page 3)** • **Current statement:** "*Stop certolizumab pegol at 16 weeks if the psoriasis has not responded adequately. An adequate response is defined as:* o *a 75% reduction in the PASI score (PASI 75) from when treatment started or* o *a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started."* • **Requested revision:** "*Stop or consider escalating the dose of certolizumab pegol at 16 weeks if the psoriasis has not responded adequately. An adequate response is defined as:* o *a 75% reduction in the PASI score (PASI 75) from when treatment started or* o *a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started.* *Account for the possibility of dose escalation only if there is a commercial arrangement in place in addition to the agreed PAS. (See Section 3.21)."*

	Section 3.21 (page 19) UCB considers that the submitted evidence, including the new analyses, are relevant evidence for the discussions at the second Committee meeting and consideration in the decision making, and thus should be reflected in Section 3.21. Furthermore, the cost-effectiveness analyses of the CZP escalation strategy considered by the ERG and UCB clearly indicate that there remains uncertainty around the true treatment costs of increasing the dose from 200 mg to 400mg of certolizumab pegol and that commercial arrangements would have an impact on relative costs – a conclusion which should also be considered in the decision making and thus reflected in the ACD.
7	**Section 1.5 (page 4):** The current recommendations state that "*The choice between certolizumab pegol or another biological treatment*….", inaccurately implying that several biologic options have been assessed during this appraisal, in addition to certolizumab pegol. UCB considers that there is potential for ambiguity and bias against the use of certolizumab pegol and this recommendation is built on statements used in multiple technology appraisals and not consistent with those from recent single technology appraisals in psoriasis. For instance, the recent NICE TA521 (guselkumab for treating moderate to severe plaque psoriasis) states "*If patients and their clinicians consider guselkumab to be one of a range of suitable treatments, including ixekizumab and secukinumab, the least costly (taking into account administration costs and commercial arrangements) should be chosen*." Furthermore there is ambiguity with respect to the basis upon which a treatment is considered "suitable" and UCB believe that greater emphasis should be placed upon the importance of clinical factors when patients and clinicians are selecting a treatment. Where multiple treatment options are "suitable", it may be that a particular treatment or treatments offer greater potential clinical value to patients, or are associated with unique benefits. The ACD states that the Appraisal Committee is interested in receiving comments on whether recommendations are a sound and suitable basis for guidance to the NHS. In this regard, UCB therefore requests that the Committee consider amending this recommendation so that it is consistent with previous guidance. **Suggested revisions, Section 1.5 (page 4)** • **Current statement:** "*The choice between certolizumab pegol or another biological treatment should be made after discussion between the patient and their healthcare professional about the advantages and disadvantages of the treatments available. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage, price per dose and commercial arrangements*." • **Requested revision:** "*<u>If patients and their clinicians consider certolizumab pegol to be one of a range of suitable biologic treatments, the clinical choice should be made after discussion</u> about the advantages and disadvantages of the treatments available. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage, price per dose and commercial arrangements)."*
8	**Section 1.1 (page 3)** In Section 1.1 (page 3), the ACD states that "*Certolizumab pegol (200 mg) is recommended as an option for treating plaque psoriasis in adults*." UCB asks that this statement is updated to remove reference to 200 mg specifically. As per the certolizumab pegol Summary of Product Characteristics, "*The recommended starting dose of Cimzia for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4.*"[11] Only after the loading dose (equivalent to 400 mg Q2W), is certolizumab pegol administered at a dose of 200 mg Q2W. Reference in Section 1.1 to 200 mg has the potential to cause confusion and advocate use of certolizumab pegol without loading dose, contrary to the approved summary of product characteristics. Section 1.1 also states that use of certolizumab pegol is subject to the condition that "*The company provides the drug according to the commercial arrangement.*" UCB asks that Section 1.1 is updated to refer to the Patient Access Scheme, instead of a commercial arrangement, in order to ensure alignment with UCB's company submission, and previous NICE recommendations for certolizumab pegol, for active psoriatic arthritis,[12] rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor,[13] rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed[14] and axial spondylarthritis.[15] **Suggested revisions, Section 1.1 (page 3)**

	• **Current statement:** *"Certolizumab pegol (200 mg) is recommended as an option for treating plaque psoriasis in adults, only if:…The company provides the drug according to the commercial arrangement"* • **Requested revision:** *"Certolizumab pegol is recommended as an option for treating plaque psoriasis in adults, only if:…The company provides the drug according to the Patient Access Scheme."*
9	**Section 3.7 (page 10)** With regards to the Company's base-case network meta-analysis, Section 3.7 (page 10) of the ACD states that "*It showed that certolizumab pegol resulted in PASI 75 response rates that were:* • *Higher (but not statistically significantly so) than the biologicals with the same mechanism of action (that is, the TNF-alpha inhibitors, adalimumab and etanercept)* • *Statistically significantly higher than etanercept"* UCB believes that this statement could cause confusion with respect to the NMA results against etanercept. Since certolizumab pegol was associated with statistically significantly higher PASI75 response rates compared to etanercept according to the base-case network meta-analysis, UCB suggests that the mention of etanercept is removed from the first bullet point. The revisions requested by UCB are detailed below: **Suggested revisions, Section 3.7 (page 10)** • **Current statement:** *"It showed that certolizumab pegol resulted in PASI 75 response rates that were:* o *higher (but not statistically significantly so) than the biologicals with the same mechanism of action (that is, the TNF-alpha inhibitors, adalimumab and etanercept)* o *statistically significantly higher than etanercept"* • **Requested revision:** *"It showed that certolizumab pegol resulted in PASI 75 response rates that were:* o *higher (but not statistically significantly so) than the biologicals with the same mechanism of action (that is the TNF-alpha inhibitor, adalimumab)* o *statistically significantly higher than etanercept"*
10	**Section 3.5 (page 9)** The ACD suggests in Section 3.5 (page 9) that "*none of the patients in the [certolizumab pegol] clinical trials had previously had phototherapy*". However, data presented in the company submission show that between [redacted] and [redacted] of patients in each of the treatment arms in all three trials (CIMPASI-1, CIMPASI-2 and CIMPACT) had received prior chemophototherapy or phototherapy. According to data presented in the Form B appendices and in Table 12 below, the same is also true when the data for all three trials is pooled. **Table 9: Baseline characteristics for patients – Proportion of patients who had received prior chemotherapy or phototherapy (ITT population Pool E1)** **Prior chemotherapy or phototherapy, n (%)** | **Placebo (n=157)** | **CZP 200 mg Q2W (n=351)** | **CZP 400 mg Q2W (n=342)** **Yes** | [redacted] | [redacted] | [redacted] **No** | [redacted] | [redacted] | [redacted] **Abbreviations:** CZP: certolizumab pegol; Q2W: every two weeks. Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1). **Source:** UCB Cimzia Plaque Psoriasis Integrated Summary of Efficacy.[16] UCB therefore requests that the incorrect statement is removed from the ACD, as suggested below. **Suggested revisions, Section 3.5 (page 9)** • **Current statement: "***The company stated that, in the CIMPASI and CIMPACT trials, similar PASI 75 response rates were reported in subgroups of patients who had previously had systemic treatment or phototherapy compared with those who had not. The committee*

	noted that the subgroup of patients who had not had systemic non-biological treatment reflected the company's proposed positioning of certolizumab pegol at an earlier setting than that for biologicals in the NHS. The exception was that none of the patients in the clinical trials had previously had phototherapy." • **Requested revision: "***The company stated that, in the CIMPASI and CIMPACT trials, similar PASI 75 response rates were reported in subgroups of patients who had previously had systemic treatment or phototherapy compared with those who had not. The committee noted that the subgroup of patients who had not had systemic non-biological treatment reflected the company's proposed positioning of certolizumab pegol at an earlier setting than that for biologicals in the NHS. [Final sentence deleted.]*"

References

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Appendix 1: Adjustments to efficacy assumptions for new analyses

The efficacy assumptions informing the previous analyses (the ERG analysis quoted in the ACD and the UCB proforma response analysis) are as outlined in Table X (note: this is a direct copy of Table X in the main body of this response).

Table 10: Efficacy sources for modelling 1st line and 2nd line in the ERG's dose escalation analysis presented in the ACD (ICER >£500,000 per QALY gained)

	CZP dose escalation strategy *(CZP 200mg > CZP 400mg > BSC > BSC > BSC)*	**"Switch" to UST 90mg strategy** *(CZP 200mg > UST90 > BSC > BSC > BSC)*
1st line	CZP 200mg efficacy based on results of NMA	CZP 200mg efficacy based on results of NMA
2nd line	CZP 400mg efficacy based on weighted average of: • *For the proportion of patients considered to be partial responders (PASI 50-74) to CZP 200mg:* clinical data provided by UCB for efficacy of CZP 400mg in the population of partial responders (PASI 50-74) to CZP 200mg from the CIMPACT study • *For the proportion of patients considered to be non-responders (PASI <50) to CZP 200mg:* UST 90mg efficacy based on results of NMA, in order to model that non-responders to CZP 200mg would switch to UST 90mg rather than escalate	UST 90mg efficacy based on results of NMA

A summary of the efficacy assumptions in the new analyses are provided in Table 11 (for the analyses that align to the CZP CIMPACT partial responder efficacy) and Table 12 (for the analyses that align to NMA-based efficacy).

Table 11: Efficacy sources for modelling 1st line and 2nd line – analyses aligning to CZP 400mg CIMPACT partial responders efficacy

	CZP dose escalation strategy (no differences versus ERG analysis and UCB proforma response [i.e. no changes versus Table 10])	**Comparator "switch" strategy** (differences versus ERG approach to modelling "switch" to UST 90mg strategy in Table 10 highlighted bold)	**Comparator (ADA) dose escalation strategy** (differences versus modelling of ADA escalation in UCB proforma response highlighted in bold)
1st line	CZP 200mg efficacy based on results of NMA	CZP 200mg efficacy based on results of NMA	ADA/UST45/UST90 efficacy based on results of NMA
2nd line	CZP 400mg efficacy based on weighted average of: • *For the proportion of patients considered to be partial responders (PASI 50-74) to CZP 200mg:* clinical data provided by UCB for efficacy of CZP 400mg in the population of partial responders (PASI 50-74) to CZP 200mg from the CIMPACT study • *For the proportion of patients considered to be non-responders (PASI <50) to CZP 200mg:* UST 90mg efficacy based on results of NMA, in order to model that non-responders to CZP 200mg would switch to UST 90mg rather than escalate	**UST 90mg (or other 'switch treatment' e.g. SEC, IXE) efficacy based on weighted average of:** • ***For the proportion of patients considered to be partial responders (PASI 50-74) to CZP 200mg:* clinical data provided by UCB for efficacy of CZP 400mg in the population of partial responders (PASI 50-74) to CZP 200mg from the CIMPACT study. This therefore assumes that the efficacy of UST 90mg (or other 'switch treatment' e.g. SEC, IXE) in partial responders is better reflected by the efficacy of CZP 400mg in partial responders than by the NMA results for the switch therapy** • ***For the proportion of patients considered to be non-responders (PASI <50) to CZP 200mg*: UST 90mg (or other 'switch treatment' e.g. SEC, IXE) efficacy based on results of NMA**	**Escalated ADA efficacy based on weighted average of:** • ***For the proportion of patients considered to be partial responders (PASI 50-74) to ADA 40mg:* assumed these patients receive escalated ADA 80mg, with efficacy based on clinical data provided by UCB for efficacy of CZP 400mg in the population of partial responders (PASI 50-74) to CZP 200mg from the CIMPACT study.** • ***For the proportion of patients considered to be non-responders (PASI <50) to ADA*: assumed these patients switch to UST 90mg*, with efficacy for second-line UST 90mg based on results of NMA for UST**

*This is the same assumption as applied to the CZP arm by the ERG when the ERG incorporated the CIMPACT partial responder data and modelled non-responders and partial responders separately for the CZP arm

Table 12: Efficacy sources for modelling 1st line and 2nd line – analyses aligning to NMA-based efficacy

	CZP dose escalation strategy (differences versus ERG analysis and UCB proforma response highlighted bold)	**Comparator "switch" strategy** (differences versus ERG approach to modelling "switch" to UST 90mg strategy in Table 10 highlighted bold)	**Comparator (ADA) dose escalation strategy** (differences versus modelling of ADA escalation in UCB proforma response highlighted in bold)
1st line	CZP 200mg efficacy based on results of NMA	CZP 200mg efficacy based on results of NMA	ADA/UST45/UST90 efficacy based on results of NMA
2nd line	CZP 400mg efficacy based on weighted average of: • ***For the proportion of patients considered to be partial responders (PASI 50-74) to CZP 200mg:* CZP 400mg efficacy based on results of the NMA** • *For the proportion of patients considered to be non-responders (PASI <50) to CZP 200mg:* UST 90mg efficacy based on results of NMA, in order to model that non-responders to CZP 200mg would switch to UST 90mg rather than escalate	UST 90mg (or other 'switch treatment' e.g. SEC, IXE) efficacy based on weighted average of: • *For the proportion of patients considered to be partial responders (PASI 50-74) to CZP 200mg:* NMA results for UST 90mg (or other 'switch treatment' e.g. SEC, IXE) • *For the proportion of patients considered to be non-responders (PASI <50) to CZP 200mg*: NMA results for UST 90mg (or other 'switch treatment' e.g. SEC, IXE) *Note that the ERG approach did not explicitly separate into partial responders and non-responders for the switch therapy, but as the new analysis treats these two groups the same there is effectively no difference versus the ERG approach*	**Escalated ADA efficacy based on weighted average of:** • ***For the proportion of patients considered to be partial responders (PASI 50-74) to ADA 40mg:* assumed these patients receive escalated ADA 80mg, with efficacy based on results of the NMA for ADA 80mg.** • ***For the proportion of patients considered to be non-responders (PASI <50) to ADA 40mg*: assumed these patients switch to UST 90mg*, with efficacy for second-line UST 90mg based on results of NMA for UST** *Note that this differs to the UCB proforma response approach, as in the UCB proforma response the analysis assumed that all patients who discontinued ADA 40mg moved to second-line ADA 80mg (there was no separation of partial and non-responders)*

*This is the same assumption as applied to the CZP arm by the ERG when the ERG incorporated the CIMPACT partial responder data and modelled non-responders and partial responders separately for the CZP arm

Appendix 2: Summary of sequences modelled in the UCB and ERG analyses

	1st line	2nd line	3rd line	4th line	5th line	Note on efficacy assumptions in 2nd line	
ERG alternative basecase (ERG report and Addendum)	**CZP200**	**CZP 400** (if partial R) **UST 90** (if non-R)	BSC	BSC	BSC	CZP 400mg CIMPACT partial responder data used for partial responders; UST 90mg NMA efficacy used for non-responders	
	CZP200	**UST 90**	BSC	BSC	BSC	UST 90mg NMA efficacy used for all patients; no differentiation of non-responders and partial responders	
UCB latest basecase (Proforma response to ERG report)	**CZP200**	**CZP 400** (if partial R) **UST 90** (if non-R)	UST 90	IFX	BSC	CZP 400mg CIMPACT partial responder data used for partial responders; UST 90mg NMA efficacy used for non-responders	
	ADA40	**ADA 80**	UST 90	IFX	BSC	ADA 80mg efficacy based on 1.5x ADA 40mg NMA efficacy, as per original submission	
UCB new scenario analyses (response to ACD)	**Comparison to ADA escalation - sequences**					**Analysis aligning to CZP 400mg CIMPACT efficacy**	**Analysis aligning to NMA efficacy**
	CZP200	**CZP 400** (if partial R) **UST 90** (if non-R)	UST 90	IFX	BSC	Same as ERG report and UCB proforma response	CZP 400mg efficacy adjusted to CZP 400mg NMA efficacy; UST 90mg NMA response for non-responders
	ADA40	**ADA 80 (**if partial R) **UST 90** (if non-R)	UST 90	IFX	BSC	ADA 80mg aligned to CIMPACT; UST 90mg NMA response for non-responders	ADA 80mg efficacy as per UCB proforma response; UST 90mg NMA response for non-responders
	Comparison to ADA escalation – no sequences						
	CZP200	**CZP 400** (if partial R) **UST 90** (if non-R)	BSC	BSC	BSC	Same as ERG report and UCB proforma response	CZP 400mg efficacy adjusted to CZP 400mg NMA efficacy; UST 90mg NMA response for non-responders
	ADA40	**ADA 80 (**if partial R) **UST 90** (if non-R)	BSC	BSC	BSC	ADA 80mg aligned to CIMPACT; UST 90mg NMA response for non-responders	ADA 80mg efficacy as per UCB proforma response; UST 90mg NMA response for non-responders
	Comparison to switch strategy - sequences						
	CZP200	**CZP 400** (if partial R) **UST 90** (if non-R)	UST 90	IFX	BSC	Same as ERG report and UCB proforma response	CZP 400mg efficacy adjusted to CZP 400mg NMA efficacy; UST 90mg NMA response for non-responders
	CZP200	**SEC** (if partial R or non-R)	UST90	IFX	BSC	SEC efficacy in partial responders aligned to CZP CIMPACT efficacy; SEC efficacy in non-responders based on SEC NMA response	SEC efficacy in partial responders and non-responders based on SEC NMA response
	CZP200	**IXE** (if partial R or non-R)	UST90	IFX	BSC	IXE efficacy in partial responders aligned to CZP CIMPACT efficacy; IXE efficacy in non-responders based on IXE NMA response	IXE efficacy in partial responders and non-responders based on IXE NMA response

Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

Consultation on the appraisal consultation document – deadline for comments 5pm on **4 January 2019 email:** TACommB@nice.org.uk/NICE DOCS

	Comparison to switch strategy – no sequences						
	CZP200	**CZP 400** (if partial R) **UST 90** (if non-R)	BSC	BSC	BSC	Same as ERG report and UCB proforma response	CZP 400mg efficacy adjusted to CZP 400mg NMA efficacy; UST 90mg NMA response for non-responders
	CZP200	**SEC** (if partial R or non-R)	BSC	BSC	BSC	SEC efficacy in partial responders aligned to CZP CIMPACT efficacy; SEC efficacy in non-responders based on SEC NMA response	SEC efficacy in partial responders and non-responders based on SEC NMA response
	CZP200	**IXE** (if partial R or non-R)	BSC	BSC	BSC	IXE efficacy in partial responders aligned to CZP CIMPACT efficacy; IXE efficacy in non-responders based on IXE NMA response	IXE efficacy in partial responders and non-responders based on IXE NMA response
	CZP200	**UST 90** (if partial R or non-R)	BSC	BSC	BSC	UST 90mg efficacy in partial responders aligned to CZP CIMPACT efficacy; UST 90mg efficacy in non-responders based on UST 90mg NMA response	UST 90mg efficacy in partial responders and non-responders based on UST 90mg NMA response

Appendix 3: Full results of new scenario analyses

Table 13: New scenario cost effectiveness analyses: comparisons to ADA escalation - aligning to CZP 400mg CIMPACT partial responders efficacy

First line therapy	Subsequent sequence	Total		Incremental (CZP escalation vs comparator)		ICER CZP escalation versus comparator
		QALYs	Costs	QALYs	Costs	
Modelling sequences of treatments						
CZP 200mg	CZP 400mg, UST 90mg, IFX, BSC	[redacted]	[redacted]			
ADA 40mg	ADA 80mg, UST 90mg, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£22,370
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)						
CZP 200mg	CZP 400mg, BSC, BSC, BSC	[redacted]	[redacted]			
ADA 40mg	ADA 80mg, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£35,481

Table 14: New scenario cost effectiveness analyses: comparisons to ADA escalation - aligning to NMA efficacy

First line therapy	Subsequent sequence	Total		Incremental (CZP escalation vs comparator)		ICER CZP escalation versus comparator
		QALYs	Costs	QALYs	Costs	
Modelling sequences of treatments						
CZP 200mg	CZP 400mg, UST 90mg, IFX, BSC	[redacted]	[redacted]			
ADA 40mg	ADA 80mg, UST 90mg, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£28,354
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)						
CZP 200mg	CZP 400mg, BSC, BSC, BSC	[redacted]	[redacted]			
ADA 40mg	ADA 80mg, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£39,489

Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

Consultation on the appraisal consultation document – deadline for comments 5pm on **4 January 2019 email:** TACommB@nice.org.uk/NICE DOCS

Table 15: New scenario cost effectiveness analyses: comparisons to switch strategies - aligning to CZP 400mg CIMPACT partial responders efficacy

First line therapy	Subsequent sequence	Total		Incremental (CZP escalation vs comparator)		ICER CZP escalation versus comparator
		QALYs	Costs	QALYs	Costs	
Modelling sequences of treatments						
CZP 200mg	CZP 400mg, UST 90mg, IFX, BSC	[redacted]	[redacted]			
CZP 200mg	SEC, UST 90mg, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£147,965 (SW)
CZP 200mg	IXE, UST 90mg, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£200,461 (SW)
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)						
CZP 200mg	CZP 400mg, BSC, BSC, BSC	[redacted]	[redacted]			
CZP 200mg	SEC, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£148,126 (SW)
CZP 200mg	IXE, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£201,308 (SW)
CZP 200mg	UST90, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£523,460

Table 16: New scenario cost effectiveness analyses: comparisons to switch strategies - aligning to NMA efficacy

First line therapy	Subsequent sequence	Total		Incremental (CZP escalation vs comparator)		ICER CZP escalation versus comparator
		QALYs	Costs	QALYs	Costs	
Modelling sequences of treatments						
CZP 200mg	CZP 400mg, UST 90mg, IFX, BSC	[redacted]	[redacted]			
CZP 200mg	SEC, UST 90mg, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£134,435 (SW)
CZP 200mg	IXE, UST 90mg, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£132,245 (SW)

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Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

Consultation on the appraisal consultation document – deadline for comments 5pm on **4 January 2019 email:** TACommB@nice.org.uk/NICE DOCS

Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)						
CZP 200mg	CZP 400mg, BSC, BSC, BSC	[redacted]	[redacted]			
CZP 200mg	SEC, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£133,868 (SW)
CZP 200mg	IXE, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£130,462 (SW)
CZP 200mg	UST90, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£313,525

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Appendix 4: Full results of new scenario analyses ([redacted])

Table 17: New scenario cost effectiveness analyses: comparisons to ADA escalation - aligning to CZP 400mg CIMPACT partial responders efficacy

First line therapy	Subsequent sequence	Total		Incremental (CZP escalation vs comparator)		ICER CZP escalation versus comparator
		QALYs	Costs	QALYs	Costs	
Modelling sequences of treatments						
CZP 200mg	CZP 400mg, UST 90mg, IFX, BSC	[redacted]	[redacted]			
ADA 40mg	ADA 80mg, UST 90mg, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	CZP dominates
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)						
CZP 200mg	CZP 400mg, BSC, BSC, BSC	[redacted]	[redacted]			
ADA 40mg	ADA 80mg, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	CZP dominates

Table 18: New scenario cost effectiveness analyses: comparisons to ADA escalation - aligning to NMA efficacy

First line therapy	Subsequent sequence	Total		Incremental (CZP escalation vs comparator)		ICER CZP escalation versus comparator
		QALYs	Costs	QALYs	Costs	
Modelling sequences of treatments						
CZP 200mg	CZP 400mg, UST 90mg, IFX, BSC	[redacted]	[redacted]			
ADA 40mg	ADA 80mg, UST 90mg, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	CZP dominates
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)						
CZP 200mg	CZP 400mg, BSC, BSC, BSC	[redacted]	[redacted]			
ADA 40mg	ADA 80mg, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	CZP dominates

Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

Consultation on the appraisal consultation document – deadline for comments 5pm on **4 January 2019 email:** TACommB@nice.org.uk/NICE DOCS

Table 19: New scenario cost effectiveness analyses: comparisons to switch strategies - aligning to CZP 400mg CIMPACT partial responders efficacy

First line therapy	Subsequent sequence	Total		Incremental (CZP escalation vs comparator)		ICER CZP escalation versus comparator
		QALYs	Costs	QALYs	Costs	
Modelling sequences of treatments						
CZP 200mg	CZP 400mg, UST 90mg, IFX, BSC	[redacted]	[redacted]			
CZP 200mg	SEC, UST 90mg, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£944,479 (SW)
CZP 200mg	IXE, UST 90mg, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£884,443 (SW)
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)						
CZP 200mg	CZP 400mg, BSC, BSC, BSC	[redacted]	[redacted]			
CZP 200mg	SEC, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£948,659 (SW)
CZP 200mg	IXE, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£891,737 (SW)
CZP 200mg	UST90, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£19,229

Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

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Table 20: New scenario cost effectiveness analyses: comparisons to switch strategies - aligning to NMA efficacy

First line therapy	Subsequent sequence	Total		Incremental (CZP escalation vs comparator)		ICER CZP escalation versus comparator
		QALYs	Costs	QALYs	Costs	
Modelling sequences of treatments						
CZP 200mg	CZP 400mg, UST 90mg, IFX, BSC	[redacted]	[redacted]			
CZP 200mg	SEC, UST 90mg, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£857,370 (SW)
CZP 200mg	IXE, UST 90mg, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£521,946 (SW)
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)						
CZP 200mg	CZP 400mg, BSC, BSC, BSC	[redacted]	[redacted]			
CZP 200mg	SEC, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£844,154 (SW)
CZP 200mg	IXE, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£495,350 (SW)
CZP 200mg	UST90, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£23,760

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Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Psoriasis and Psoriatic Arthritis Alliance
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

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Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We welcome the positive recommendation of certolizumab pegol for treating chronic plaque psoriasis. People living psoriasis will be reassured that there will be further options and choice for them when other therapies begin to lose efficacy.
2	
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**British Association of Dermatologists**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**N/A**]
Name of commentator person completing form:	[[redacted] **on behalf of the British Association of Dermatologists' Therapy & Guidelines sub-committee**]

Comment number	**Comments** Insert each comment in a new row.

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Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We would like to raise the point again that listing PUVA as a suitable treatment in the context of current treatment modalities is not appropriate and is frequently misinterpreted by CCGs as meaning clinicians have to justify or even use PUVA in their biologics pathway. This is bad practice and NICE are, by not changing this 'standard' wording, supporting this ongoing bad practice.
2	
3	
4	
5	

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**LEO Pharma**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We note that fourth line treatments Apremilast and Dimethyl fumarate were not considered as comparators for this appraisal. Bearing in mind the proposed positioning by the company for Certolizumab i.e as an alternative to: systemic non-biological treatments such as methotrexate, ciclosporin and acitretin, and following topical therapy and phototherapy; or biological treatments , the analysis seems incomplete without comparison versus Apremilast and Dimethyl Fumarate that are used as alternatives to biologics. Both these agents have been 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 technological appraisals (STAs) for Brodalumab included these treatments as comparators (Guselkumab was a fast track appraisal so did not require comparison to all available treatments) , thus the Certolizumab 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.
2	The committee states on page 17 that *people with psoriasis, particularly those whose psoriasis does not respond to adalimumab, would value the option of an alternative TNF-alpha inhibitor that was more effective than etanercept and could be used during pregnancy.* We are concerned that this may imply cycling through multiple anti-tnfs before moving onto other agents. Whilst PASI 75 is still being used as criteria to determine clinical effectiveness for biologics, with the more recent advances in newer classes of biological agents, PASI levels of 90 & 100 are now achievable for a greater number of patients compared to those seen with use of anti-tnfs. Having another anti-tnf like certolizumab , whilst providing choice especially during pregnancy, should not be used to delay use of more clinically effective treatments (that have also demonstrated cost-effectiveness), in the cohort of patients who may have already used an existing anti-tnf like adalimumab but not achieved adequate response.
3	We agree with the proposal that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance.

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more

Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

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information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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ACD - Consultees & Commentators: Psoriasis (plaque, chronic) - certolizumab pegol [ID1232]

Having looked at the recommendations on p3-4, there is no mention of use of the 400mg dose of certolizumab pegol.

There is a proven benefit and clinical value with use of the 400mg dose in initial non or inadequate responders. In patients where the psoriasis has not initially responded to the 200mg dose, there is the opportunity to escalate to 400mg 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 400mg dose if there is an initial inadequate response, if the situation is cost-effective or there are local agreements in place.

Dr Hector Chinoy
Consultant Rheumatologist
4th Dec 2018

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Organisation	
Location	England
Conflict	I have acted as consultant to UCB
Notes	
Comments on the ACD:	
I understand that certolizumab has not currently been approved at 400mg. I just wanted to say as a dermatologist responsible for patients with severe psoriasis that frequently a higher dose than is identifed in clinical trials is needed in the hard to treat population. This has been recognised with several other biologics for psoriasis including ustekinumab and adalimumab which now allow doubling of the dose. Ability to vary the dose is very helpful in practice in the absence of any data showing an increase in adverse events.	

Name	[redacted]
Role	NHS Professional
Other role	Consultant Dermatologist
Organisation	
Location	England
Conflict	I was a member of the appraisal committee for this medication, and acted as expert (dermatology) medical advisor.
Notes	
Comments on the ACD:	
s this recommendation pertains only to the CZP 200mg and it is mandated to stop if the response is not adequate it prohibits clinicians using the 400mg Q2W dose when we feel it is clinically needed. In current practice a subset of patients treated with biologics may have a sub-optimal response and might require dose escalation of therapy as a measure to improve efficacy. The phase III data for CZP in PSO shows a higher efficacy in the patients that are initiated on 400mg Q2W versus the 200mg Q2W and increasing efficacy in those patients that are escalated from 200mg Q2W to 400mg Q2W when their PASI response is below 75. Therefore, it would be beneficial to some patients if the use of the 400mg Q2W was allowed by amending the continuation criteria (section1.2) to allow dose escalation so that patients with a suboptimal response (PASI response of less than 75) could benefit from increased response to treatment. This 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. " "In my opinion the benefit of the escalation from 200mg Q2W to 400mg Q2W has not	

been fully represented in the ACD. As mentioned above the phase III data for CZP in PSO shows a higher efficacy in the patients that are initiated on 400mg Q2W versus the 200mg Q2W and increasing efficacy in those patients that are escalated from 200mg Q2W to 400mg Q2W when their PASI response is below 75.

The data shows clear benefits in efficacy of increasing the dose of certolizumab pegol and it is important that this is accounted for in the interpretation of the evidence within the ACD and reflected in the recommendation.
"
"The recommendation states that Certolizumab and Adalimumab can be used for pregnancy and breastfeeding. It is great to have a number of choices of biologic that can be used in this patient group. However, it is important to acknowledge the significant differences in the structure of the antibodies, with Adalimumab retaining and Fc region compared to Certolizumab. The evidence is that Adalimumab crosses the placenta1, 2, and this may be of importance in its clinical use3.

1) Mahadevan et al. Clin Gastroenterol Hepatol. 2013 March ; 11(3): 286“e24. doi:10.1016/j.cgh.2012.11.011
2) Flint et al. Rheumatology, Volume 55, Issue 9, 1 September 2016, Pages 1693“1697
3) 3) Adalimumab SmPC. http://www(.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf.

Name	[redacted]
Role	NHS Professional
Other role	Dermatologist
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ACD:	
Certolizumab will provide a useful option in a number of patients most notably: 1. Pregnant females 2. Patients for whom a secondary non-response has been observed with adalimumab or other TNF inhibitor 3. Patients with a suboptimal response to other TNF inhibitors.	

Name	[redacted]
Role	NHS Professional
Other role	SWL Commissioning Pharmacist
Organisation	NEL (formerly NEL CSU)
Location	England
Conflict	No
Notes	
Comments on the ACD:	
We welcome that the dose of 200mg is highlighted as the recommended dose in 1.1	

esp as dose escalation to 400mg is mentioned in Chapter 2 as part of the SPC. Disease has not responded to ciclosporin, methotrexate and PUVA, or these options are contraindicated or not tolerated... This is in line with all other TAs but appears out of sync with feedback received from local clinicians who seem to consider UVB as an alternative. UVB is mentioned in the consultation document slides as part of the treatment pathway but not considered in the TA. Furthermore, the recommendation does not consider patients who are unable to attend PUVA due to work commitments whereas this is mentioned in the NICE CG.
Lack of recommendations on sequential treatment and place in therapy. This will cause problems with providers as they invariably interpret that the drug should be available as an option for any patient fulfilling the criteria in section 1.1 (regardless whether this is 1st, 2nd, 3rd or even 4th line). We would appreciate a clear recommendation as to where in the biologic pathway the treatment sits.

Single Technology Appraisal (STA)

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

ERG commentary on the response submitted by the company to the ACD

Produced by **CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD**

Date **15/01/2019**

Note on the text

All commercial-in-confidence (CIC) and academic-in-confidence (AIC) data are redacted.

1 Overview

The evidence review group (ERG) was requested by NICE to provide validity checks and a critique of the additional dose escalation scenarios submitted by the company in response to the appraisal consultation document (ACD). These additional analyses pertain to the scenario where patients on certolizumab (CZP) 200mg who achieve a partial response at week 16 may continue on CZP with a higher dose of 400mg, henceforth referred to as a dose escalation scenario.

Due to the limited time available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. However, the ERG has checked the implementation of any proposed changes and ensured replication of the results presented by the company.

The scenarios presented in the company's response to the ACD included cost-effectiveness results from an amended version of the ERG's base-case model, comparing:

1 A dose escalation scenario for CZP compared with a dose escalation scenario for adalimumab (ADA);
2 A dose escalation scenario for CZP compared with switching to other biologics, including ustekinumab (UST), ixekizumab (IXE) and secukinumab (SEC).

The company's revised models incorporate the ERG- and Committee-preferred utility values and the results of the updated network meta-analysis (NMA) provided by the company after the ERG's report had been submitted. However, the revised models did not incorporate the biosimilar prices for infliximab (IFX) and etanercept (ETN). This change was made by the ERG and accepted by the Committee in the ACD, and so the ERG has provided additional results of the analyses with these costs applied. ADA biosimilar products are now available, and the ERG has provided results with a discount to the list price of Humira (ADA originator product) to demonstrate the impact on cost-effectiveness with a lower price of ADA.

2 ERG commentary on the amended company scenarios

2.1 Company amendments to the ERG model

Within their response to the ACD, the company raised a number of concerns regarding the assumptions made in the dose escalation scenarios, which they attempted to address through the presentation of additional analyses. These are discussed by the ERG in turn below, and include:

- Additional comparisons to other switching strategies (to SEC and IXE after CZP 200 mg, in addition to UST as presented in the original dose escalation scenario);
- Additional comparisons to an ADA dose escalation scenario;
- Explore the impact of aligning efficacy sources between the CZP escalation and comparator arms (CZP 400mg modelled using PASI response rates from the NMA or from CIMPACT);
- The use of treatment sequences to estimate cost-effectiveness over a patient lifetime;
- The application of [redacted].

Additional switching strategies

The company voiced concerns that the ACD currently fails to acknowledge that a switch to UST 90mg after non-response to CZP 200mg is not the only option that might be considered clinically appropriate. The ERG does not consider it unreasonable to compare sequences with other therapies after CZP, and acknowledges the variability in treatment pathways that patients may follow. Other biologics such as brodalumab and guselkumab that have recently been recommended by NICE may also have been appropriate alternatives. The ERG highlights that switching to UST aligns with the company's original base-case, and that clinical advice to the ERG supports this assumption.

It appears from the results in Table 5 that the cost-effectiveness of a switching scenario versus a dose escalation scenario is dependent on the relative effectiveness of each option. IXE and SEC are associated with a higher rate of responders at their decision point at 12 weeks than CZP 400mg at 16 weeks. Therefore, CZP dose escalation scenarios were associated with fewer QALY gained compared with switching to IXE or SEC. The ERG expects that a similar pattern would be observed with other biologics e.g. brodalumab and guselkumab. Meanwhile, UST has a marginally lower rate of response at 16 weeks than CZP 400mg, and as such this sequence provides fewer QALYs than the CZP dose escalation scenario.

Furthermore, these additional sequences where patients switch to IXE or to SEC after CZP 200mg have been compared to a CZP dose escalation scenario in which non-responders switch to UST i.e sequence A compared with sequence B or C (Table 1). However, the ERG considers the more appropriate counterfactual to be one where non-responders switch to IXE or to SEC in each analysis respectively, and consider the pairwise comparisons of sequence B versus D, and C versus E. The ERG has included the results of these additional analyses in Table 6.

Table 1 Summary of treatment switching scenarios

	Dose escalation sequence with UST (A)	**IXE switch sequence (B)**	**SEC switch sequence (C)**	**Dose escalation sequence with IXE (D)**	**Dose escalation sequence with SEC (E)**
Scenario	Current baseline strategy for each analysis	Company compared with sequence A	Company compared with sequence A	More appropriate counterfactual to sequence B	More appropriate counterfactual to sequence C
1st line	CZP 200mg	CZP 200mg	CZP 200mg	CZP 200mg	CZP 200mg
2nd line	Non-responders go to UST 90mg Partial responders go to CZP 400mg	IXE	SEC	Non-responders go to IXE Partial responders go to CZP 400mg	Non-responders go to SEC Partial responders go to CZP 400mg
3rd line	Modeling sequences: UST 90 Head-to-head comparison: BSC	Modeling sequences: UST 90 Head-to-head comparison: BSC	Modeling sequences: UST 90 Head-to-head comparison: BSC	Modeling sequences: UST 90 Head-to-head comparison: BSC	Modeling sequences: UST 90 Head-to-head comparison: BSC
4th line	Modeling sequences: IFX Head-to-head comparison: BSC	Modeling sequences: IFX Head-to-head comparison: BSC	Modeling sequences: IFX Head-to-head comparison: BSC	Modeling sequences: IFX Head-to-head comparison: BSC	Modeling sequences: IFX Head-to-head comparison: BSC
5th line	BSC	BSC	BSC	BSC	BSC

Escalation with adalimumab

The company presented two scenarios representing ADA dose escalation, which they maintain is the appropriate comparison to a CZP dose escalation scenario. In the first scenario, it was assumed that all non-responders to ADA 20mg are escalated to ADA 40mg, and this scenario was compared with a CZP dose escalation scenario where only partial responders to CZP were dose escalated, while non-responders switched treatment to UST. In a second scenario, non-responders switched to UST, and partial responders escalated to ADA 80mg.

There are a number of limitations of the analyses of ADA dose escalation:

1. There is no trial data to support the efficacy of ADA 80mg, whether these are partial responders or non-responders to ADA40, or in those who had not previously received ADA

40mg. The company either assumed the efficacy to be equivalent to CZP 400mg in previous partial responders to CZP 200mg (estimated from CIMPACT trial data), or assumed that was equivalent to an adjustment of the ADA40 response estimated from the NMA (1.5 multiplier applied to the ADA40 PASI75 score, which in itself represents a heterogeneous mix of patients). As such, there is very significant uncertainty in the analyses of these patients.

2. No evidence was provided of widespread use of ADA dose escalation in clinical practice. While the label for ADA states patients with inadequate response to ADA 40 mg may benefit from an increase in dosage 80 mg, NICE recommended to discontinue ADA in people whose psoriasis has not responded adequately at 16 weeks. Furthermore, clinical advice to the ERG suggested dose escalation with ADA would only be commissioned at a local level if biosimilars were made available at a sufficiently reduced cost .
3. The appropriate counterfactual for a CZP dose escalation strategy would be to switch to another biologic, not a dose escalation strategy with another biologic. Clinicians would not choose a strategy on the basis that the dose could be escalated in partial-responders. As discussed in Section 6.3.7 and 5.2.4 of the original ERG report, the ERG considers the counterfactual to the proposed dose escalation strategy to be 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. These scenarios treats escalation of certolizumab as a distinct decision in a patient's treatment strategy
4. The company did not present results with biosimilar adalimumab costs applied. Adalimumab biosimilars are currently available, 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. As such, the ERG present additional analyses where the biosimilar price is 20% lower than the originator price for ADA. The price reduction for ADA may be as high as 75%[1].

Aligning efficacy sources

A scenario presented by the ERG in their original report included patients who escalated to CZP 400mg if they receive a partial response at week 16 (that is, a response between a PASI50 and PASI75 response). The efficacy for these patients after escalating was based on data from the CIMPACT trial.

Since the efficacy for other lines of therapy is based on the results of the NMA, the company expressed concerns in their response to the ACD that the use of two difference sources of data to

[1] https://www.england.nhs.uk/2018/11/nhs-set-to-save-record-300-million-on-the-nhss-highest-drug-spend/

model treatment efficacy in the sequence would result in bias in favour of the comparator sequences, in which the treatments were based solely on rates from the NMA. The use of the NMA data makes the assumption that the efficacy is the same for treatments when used as a first line treatment as when used at subsequent lines, which may overestimate the efficacy of subsequent lines, as it would be expected that efficacy of biologics would decrease with each line of therapy.

The company explored the impact of this bias by using the same efficacy source in both treatment arms in the new analyses. Two approaches for modelling the efficacy of second-line treatment in patients who were partial responders to first-line treatment are explored (Table 2).

Table 2 Efficacy sources for modelling first- and second-line treatment

	CZP dose escalation strategy	Comparator "switch" strategy	Comparator (ADA) dose escalation strategy
1st line	CZP 200mg efficacy based on results of NMA	CZP 200mg efficacy based on results of NMA	ADA 40mg efficacy based on results of NMA
2nd line	CZP 400mg efficacy based on weighted average of: *For the proportion of patients considered to be non-responders (PASI <50) to CZP 200mg:* • UST 90mg efficacy based on results of NMA, in order to model that non-responders to CZP 200mg would switch to UST 90mg rather than escalate (both scenarios) *For the proportion of patients considered to be partial responders (PASI 50-74) to CZP 200mg:* • Scenario 1: clinical data provided by UCB for efficacy of CZP 400mg in the population of partial responders (PASI 50-74) to CZP 200mg from the CIMPACT study • Scenario 2: CZP 400mg efficacy based on results of the NMA	UST 90mg (or other 'switch treatment' e.g. SEC, IXE) efficacy based on weighted average of: *For the proportion of patients considered to be non-responders (PASI <50) to CZP 200mg*: • UST 90mg (or other 'switch treatment' e.g. SEC, IXE) efficacy based on results of NMA) *For the proportion of patients considered to be partial responders (PASI 50-74) to CZP 200mg:* • Scenario 1: Assumed to be equivalent to the efficacy of CZP 400mg in the population of partial responders (PASI 50-74) to CZP 200mg from the CIMPACT study • Scenario 2: NMA results for UST 90mg (or other 'switch treatment' e.g. SEC, IXE)	Escalated ADA efficacy based on weighted average of: *For the proportion of patients considered to be non-responders (PASI <50) to ADA 40mg*: • Assumed these patients switch to UST 90mg, with efficacy for second-line UST 90mg based on results of NMA for UST *For the proportion of patients considered to be partial responders (PASI 50-74) to ADA 40mg:* • Scenario 1: assumed these patients receive escalated ADA 80mg, with efficacy assumed to be equivalent to that of CZP 400mg in the population of partial responders (PASI 50-74) to CZP 200mg from the CIMPACT study • Scenario 2: assumed these patients receive escalated ADA 80mg, with efficacy based on results of the NMA for ADA 80mg.

Given the limitations associated with the clinical data's capacity to capture efficacy over multiple lines of treatment, the ERG do not consider it unreasonable to explore a range of sources for second-line treatment, given the lack of directly applicable evidence for these treatments in this position, and the general challenges with modelling sequences of treatments in this disease area.

However, there are some major limitations with these analyses. Firstly, no evidence has been presented to suggest that the efficacy of UST, IXE, SEC or ADA 80mg in partial responders to previous treatment would be equivalent to CZP 400mg. A comparison of these treatments in the NMA suggests that IXE is associated with a higher response rates than CZP, while UST 90mg is associated with a lower rate of response. Furthermore, the use of the CIMPACT data for IXE and SEC in previous partial responders implies that previous partial responders have lower response rates than previous non-responders.

The bias arising from the use of the CIMPACT trial data alongside the NMA to model patients on second-line therapy may be overstated by the company, since patients enrolled in the CIMPACT trial were also heterogenous with respect to their previous biologics experience (much like those in the NMA). It is the view of the ERG that previous exposure to the same biologic at a difference dose would have a greater influence on efficacy than previous exposure to a different biologic. With this in mind, the ERG considers the use of the CIMPACT data more accurate for modelling CZP 400mg. Reassuringly, it appears from the results of the analyses that alternating between these two sources of data makes only a small difference to the number of QALYs and costs generated for each sequence, since these efficacy data are only applied to a proportion of second-line patients.

Sequencing

The company provided analyses both *with* treatment sequencing and *removing* treatment sequencing (i.e. all subsequent treatment options set to BSC after the escalated therapy/switch biologic), in order to assess the influence of treatment sequencing on results. This takes into account previous considerations of the ERG and the Committee, as outlined in Section 3.18 of the ACD, that "…*treatment sequences, although more likely to reflect the treatment switching seen in clinical practice, may have provided misleading cost-effectiveness estimates for certolizumab pegol*". The results presented in Table 3 to Table 6 demonstrate that modelling treatment sequences has a large impact on cost-effectiveness, with head-to-head comparisons being associated with higher ICERs.

Additionally, modelling sequences is less meaningful in an escalation strategy that models alternative treatment pathways following CZP 200mg based on whether a partial response is achieved or not. In these sequences, UST is modelled as the third line of treatment (Table 2), resulting in non-responders to CZP 200mg essentially receiving UST as both second-line and third-line points in the sequence. As such, the head-to-head comparisons avoid this by modelling BSC at third-line in the sequence.

Local pricing scenarios:

The company also present scenarios that incorporate [redacted]. The ERG does not consider it appropriate to include this assumption when making recommendations for the dose escalation

scenario, [redacted]. These scenarios are presented in the company response to the ACD, but are not replicated here.

To summarise:

- Biosimilar prices for ADA, IFX and ETN should be included in the analyses;
- It is reasonable to consider alternative biologics in switching strategies in comparison to a CZP dose escalation scenario, but the counterfactual to these should be a CZP dose escalation incorporating the alternative biologic instead of UST;
- There is no trial data for patients receiving ADA 80mg, and so results of these scenarios should be interpreted with caution;
- The appropriate counterfactual for a CZP dose escalation strategy would be to switch to another biologic instead of escalating, not a dose escalation strategy with ADA;
- The company's scenarios where the source of data for second-line therapy is aligned for second-line therapies does not adequately address the bias introduced by using CIMPACT data to model CZP 400mg;
- Head-to-head comparisons provide more meaningful results than sequencing, especially in the context of dose escalation in partial responders;
- It is not appropriate to incorporate [redacted].

2.2 Results of the company's scenarios

In their response to the ACD, the company claims that CZP dose escalation is cost-effective in 11 out of the 15 analyses presented below, assuming a cost-effectiveness threshold of £30,000 per QALY. The two noted exceptions were the comparison to ADA escalation without sequencing (with ICERs of £35,481 and £39,489, in Table 4) and the comparison to a switch to UST strategy (with ICERs of £523,460 and £313,525 in Table 5). There were a number of CZP dose escalation sequences which were associated with fewer QALYs and lower costs compared with the IXE or SEC switching scenarios (before the cPAS for IXE and SEC were applied), but had an ICER in the acceptable range of values, i.e. the CZP sequences were not effective but may be considered cost-effective. In these scenarios, the ICER can be interpreted as the cost savings per QALY lost.

These scenarios incorporate the ERG-preferred utility values, but are based on originator prices for IFX and ADA rather than the biosimilar prices, which was the committee-preferred assumption. As

such, the ERG has run additional scenarios with biosimilar price for IFX and biosimilar price for ADA (assumed to be 20%), which is substantially lower than the anticipated reduction in price.

Sequences with ADA dose escalation

Results of the ADA dose escalation scenarios are presented in Table 3 (representing an ADA non responder dose escalation scenario) and in Table 4 (representing an ADA partial responder dose-escalation scenario). The company estimated that the ICER for the ADA partial responder dose-escalation scenario ranged from £22,370 to £39,489. With biosimilar costs for ADA applied, dose escalation with CZP does not represent a cost-effective strategy in any scenario, with ICERs ranging from £67,610 upwards.

Table 3 Company scenario analyses for CZP escalation strategy versus ADA escalation strategy – all ADA 40mg escalate dose upon discontinuation (CZP with PAS) (adapted from Table 5 in ACD response)

First-line therapy	Subsequent sequence	Total		Incremental		ICER
		QALYs	Costs	QALYs	Costs	
Presented by company (based on originator prices for infliximab and etanercept)						
CZP 200mg	CZP400mg/UST, UST, IFX, BSC	[redacted]	[redacted]	-	-	-
ADA 40mg	ADA80mg, UST, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	CZP dominates
With biosimilar price for IFX and biosimilar price for ADA (assumed to be 20%)						
CZP 200mg	CZP400mg/UST, UST, IFX, BSC	[redacted]	[redacted]	-	-	-
ADA 40mg	ADA80mg, UST, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£56,112
All ADA40 switch to ADA80 after discontinuation ADA 80mg based on NMA results for ADA40 , adjusted by multiplier of 1.5. CZP 400mg data from CIMPACT used for CZP-escalated partial responders. All other comparators use NMA efficacy rates. Note the ERG has updated the terminology for second-line therapy in the CZP dose escalation sequence to reflect that a proportion of patients switch to CZP 400mg and a proportion of patients switch to UST						

Table 4 Company scenario analyses for CZP escalation strategy versus ADA escalation strategy – partial responders to ADA 40mg escalate dose after discontinuation (CZP with PAS, originator product prices) (adapted from Table 6 in ACD response)

First-line therapy	Subsequent sequence	ICER Aligning to CZP 400mg CIMPACT partial responders efficacy [1]	ICER Aligning to NMA efficacy [2]
Modelling sequences of treatments (based on originator prices)			
CZP 200mg	CZP 400mg/UST, UST 90mg, IFX, BSC	-	-

ADA 40mg	ADA 80mg/UST, UST 90mg, IFX, BSC	£22,370	£28,354
Modelling sequences of treatments (based on biosimilar prices for IFX and ADA)			
CZP 200mg	CZP 400mg/UST, UST 90mg, IFX, BSC	-	-
ADA 40mg	ADA 80mg/UST, UST 90mg, IFX, BSC	£79,587	£67,610
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC) (based on originator prices)			
CZP 200mg	CZP 400mg/UST, BSC, BSC, BSC	-	-
ADA 40mg	ADA 80mg/UST, BSC, BSC, BSC	£35,481	£39,489
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC) (based on biosimilar prices for IFX and ADA)			
CZP 200mg	CZP 400mg/UST, BSC, BSC, BSC	-	-
ADA 40mg	ADA 80mg/UST, BSC, BSC, BSC	£82,620	£72,133

[1] CZP 400mg data from CIMPACT used for CZP-escalated partial responders, ADA 80mg assumed to be equivalent to CZP 400mg data from CIMPACT

[2] CZP 400mg NMA data used for CZP-escalated partial responders, ADA80mg efficacy based on 1.5 multiplier applied to ADA40mg from the NMA.

[3] A partial responder scenario, where ADA40mg partial responders dose-escalated to ADA 80mg and non-responders switched to UST 90mg. UST 90mg NMA efficacy used for non-responders.

Note the ERG has updated the terminology for second-line therapy in the CZP dose escalation sequence to reflect that a proportion of patients switch to CZP 400mg and a proportion of patients switch to UST

Alternative switching scenarios

In their ACD response, the company also presented results for scenarios where CZP dose escalators are compared to those who switch to an alternative biologic e.g. UST 90mg, IXE or to SEC (Table 5).

The company did not present an analysis for CZP dose escalation versus a switch to UST when full sequences (i.e. including UST, IFX as third and fourth line therapy) were modelled. No explanation was given for this, but the ERG presumes that it would be due to the fact that it would result in an UST sequence with fewer lines of biologic therapies, which would be inappropriate. This situation is avoided when strategies are considered head-to-head.

Results of these analyses with the cPAS for IXE and SEC are presented in a confidential appendix to this report.

In the company's scenarios, switching to IXE or SEC was associated with a greater number of QALYs than the CZP dose escalation scenarios. As previously discussed, this is due to SEC and IXE having higher response rates than CZP 400mg, so fewer patients in the SEC and IXE (non-escalated) sequences switch to receive BSC, a treatment associated with low response rates and subsequently fewer generated QALYs. Conversely, UST 90mg has a marginally higher rate of non-response than CZP 400mg, so a dose escalation sequence resulted in a higher number QALYs.

Table 5 Company scenario analyses for CZP escalation strategy versus switch to alternative biologic (CZP with PAS, originator product prices) (adapted from Table 6 in ACD response)

Comparison	First-line therapy	Subsequent sequence	ICER Aligning to CZP 400mg CIMPACT partial responders efficacy	ICER Aligning to NMA efficacy
Modelling sequences of treatments				
CZP escalation	CZP 200mg	CZP 400mg/UST, UST 90mg, IFX, BSC	-	-
Switch to SEC	CZP 200mg	SEC, UST 90mg, IFX, BSC	£147,965 (SW*)	£134,435 (SW*)
Switch to IXE	CZP 200mg	IXE, UST 90mg, IFX, BSC	£200,461 (SW*)	£132,245 (SW*)
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)				
CZP escalation	CZP 200mg	CZP 400mg/UST, BSC, BSC, BSC	-	-
Switch to SEC	CZP 200mg	SEC, BSC, BSC, BSC	£148,126 (SW*)	£133,868 (SW*)
Switch to IXE	CZP 200mg	IXE, BSC, BSC, BSC	£201,308 (SW*)	£130,462 (SW*)
Switch to UST 90mg	CZP 200mg	UST90, BSC, BSC, BSC	£523,460	£313,525
*SW indicates a south-west ICER (i.e. CZP escalation strategy associated with lower QALYs and lower costs).				

The ERG presents additional scenarios considering the alternative counterfactuals for the IXE and SEC sequences (Table 1), and applying the biosimilar price for IFX. Only analyses modelling the first- and second-line therapies head-to-head were considered appropriate to include.

In these analyses, CZP dose escalation scenarios are dominated by IXE and SEC switching scenarios, and ICERs for CZP dose escalation compared with the UST switching strategies lay far above accepted cost-effectiveness thresholds.

Table 6 ERG scenario analyses or CZP escalation strategy versus switch to alternative biologic (CZP with PAS, biosimilar prices)

First line therapy	Subsequent sequence	ICER (CZP escalation vs comparator)	
		CZP 400mg based on CIMPACT partial responders efficacy	CZP 400mg based on NMA efficacy
Modelling no sequences (i.e. all subsequent therapies post-escalation set to BSC)			
CZP 200mg	CZP 400mg/UST, BSC, BSC, BSC	-	-
CZP 200mg	UST90, BSC, BSC, BSC	£579,068	£313,525
CZP 200mg	CZP 400mg/SEC, BSC, BSC, BSC	-	-
CZP 200mg	SEC, BSC, BSC, BSC	Dominated	Dominated
CZP 200mg	CZP 400mg/IXE, BSC, BSC, BSC	-	-
CZP 200mg	IXE, BSC, BSC, BSC	Dominated	Dominated