NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF inhibitor [ID824]

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**
   - **British Society for Rheumatology** endorsed by National Rheumatoid Arthritis Society and Royal College of Physicians
   - **Merck Sharp & Dohme**

   'No comment' response received from Department of Health and the Royal College of Nursing

3. **Evidence Review Group critique of the Company ACD response**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF inhibitor

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

Definitions:

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 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 determination (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, 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.

Comments received from consultees

Consultee	Comment [sic]	Response
UCB Pharma	**1. Use of certolizumab pegol in patients with moderate to severe disease activity** In section 1.1 (page 3) of the ACD, the committee makes the recommendation for certolizumab pegol to be used in patients with prior failure of a TNFi "*only if disease is severe*". Such wording is also used in other places of the ACD in sections 4.4 and 4.8, as well as in the summary of the committee's conclusions. UCB would like to note that as per the final scope of the current appraisal set by NICE, the population in which CZP is reviewed is patients with moderate to severe disease activity, which reflects the current marketing authorisation for CZP and is in line with the data submitted and the discussions during the scoping process. Furthermore, as indicated during the scoping workshop by the BSR representative, the eligibility criteria of "severe disease activity" only applies to the initiation of the first biologic, but not to the initiation of a second biologic in patients with inadequate response to the first TNFi. In order for a patient to be in severe disease activity after at least 6 months of the first TNFi, initiated as per the eligibility criteria indicated in TA375, the patient should have been in a highly severe/refractory disease activity at the time of starting the first biologic therapy. As such, a patient with severe disease activity who received a first TNFi and did not adequately respond to such treatment (due to failure to achieve or maintain a EULAR moderate response), may present with a DAS28<5.1 at the point of assessment of response of the first TNFi, and thus be in moderate disease activity. Consequently, such a patient, although showing inadequate response to a first biologic, would not be	Comment noted. The committee considered the request from UCB and clarified its understanding of previous guidance in TA375 and TA195. It understood that both pieces of guidance explicitly state that a first and second biologic should be started if disease is severe. However the committee considered preceding guidance and the desire for parity with existing guidance at the same point in the pathway. The committee concluded that starting a second biologic should not be limited to a DAS28 score as there are other measures of disease activity that may be used in practice. See section 4.2

Consultee	Comment [sic]	Response
	eligible for a second TNFi according to the proposed recommendation. In line with the final decision scope of the NICE appraisal and marketing authorisation for CZP, the UCB submission was based on evidence in adults with moderate to severe, active rheumatoid arthritis (RA) whose disease had not responded adequately to a TNFi. Given that the clinical benefits and cost-effectiveness of CZP presented in the UCB submission and in the ERG's independent analysis reflect the value of CZP across patients of moderate to severe disease activity, we would like to request revision of the recommendation to be aligned to the patient population that the submitted evidence supports, that is, patients with moderate to severe, active RA whose disease has not responded adequately to a TNFi.	Comment noted. The committee considered the evidence presented to them according to the comparators in the scope. The committee noted that no evidence was presented that would be considered relevant treatments for people with moderate disease activity, and as such the committee could not recommend certolizumab for people with moderate disease. See section 4.2 and 4.4 of FAD.
UBB Pharma	**2. Heterogeneity of the submitted NMA** In section 4.7 (page 9) of the ACD, the committee states that "*Heterogeneity was not appropriately accounted for. This could lead to an over-estimation of effect, favouring certolizumab pegol. The committee heard that the evidence review group (ERG) would have preferred to see random effects models throughout, rather than fixed effects models, because these can adequately capture the heterogeneity expected from the studies included in the analysis*". UCB respectfully disagrees with the statement implying that the use of a fixed effects model in the UCB network meta-analyses would lead to an over-estimation of the effect of certolizumab pegol, as this statement is unproven and not representative of the ERG's critique of the analyses, which states that the results may not *"represent genuine uncertainty"* (ERG report, page 15). To our knowledge, the ERG report does not explicitly state that the fixed effects model would yield an over-estimation of the effect of certolizumab pegol, in support of the ACD statement. As indicated in the UCB response to the ERG clarification questions (page 17) as well as the UCB submission (section 5.3.1.5, page 189), a random effects	Comment noted. The committee noted that the wording in the ACD did not accurately reflect the company or ERG critique but still maintained that there were uncertainties in the estimates from the methodology. This section has been amended (accordingly, for clarity). See section 4.6 of FAD.

Consultee	Comment [sic]	Response
	model was not considered in the base case analysis due to the limited number of studies in the network (five studies in the base case, each reporting outcomes comparing a different bDMARD versus PBO). Under such circumstance, the 'weakly informative prior information' suggested by ERG is not applicable. To provide a genuine estimate of between study variance, it may be necessary to use a strongly informative prior for this parameter in the NMA model, and any misspecification of the prior may bias the outcomes of the NMA. Hence, a fixed effects model was preferred to a random effects model in the base case in the UCB submission	
UCB Pharma	**3. Cost-effectiveness of certolizumab pegol in Population A** As outlined in the UCB response to ERG clarification question B.2 (page 30 of the UCB response), the sequence of therapies considered for population A were selected based on the expert opinion of a clinical rheumatologist, with experience in treating RA patients in clinical practice in England. The clinical expert opinion was that it would be clinically reasonable to consider certolizumab pegol (CZP) before RIT, unless contraindicated, to allow a second TNFi treatment option, before switching to another mechanism of action agent. The sequence CZP placed after RIT (where TOC + MTX is currently placed according to TA247) in Population A was considered not to be relevant to the final scope of this appraisal, and thus not included in the UCB submission. UCB recognise that one of the additional ERG scenarios of CZP instead of RIT is a relevant strategy and should therefore be explored as part of the economic analyses	Comment noted. The committee noted that placing certolizumab after rituximab and was not a relevant comparator but also noted this was true for the case for placing certolizumab before rituximab and concluded the only relevant comparison would be where certolizumab is placed instead of rituximab in the analysis for people for whom rituximab is a treatment option. See section 4.10 of FAD.
	The conservative assumption of equal treatment discontinuation rate was maintained as in the UCB submitted basecase, based on the ERG assumptions adopted in the NICE TA375,[1] as well as given the contradictory evidence on treatment duration of TNFis versus non-TNFis identified in the literature, which is further discussed below. The second assumption on the RIT retreatment cycle length of 6 months was also maintained as in the UCB submitted basecase, as supported by the SmPC and the NICE TA195[6] guidance for RIT.	Comment noted. The committee acknowledged the interpretation of the wording in the SPC for rituximab does not explicitly mean a retreatment interval of 6 months. In practice this would differ and agreed that the retreatment interval should be based on a source that studied rituximab, the REFLEX trial, which was 10.09 months

Consultee	Comment [sic]	Response
	One of the key drivers of the cost-effectiveness analysis is the assumption related to the biologic treatment duration after initial response, as indicated by the sensitivity analyses included in the UCB submission (pages 245 and 249). More specifically for Population A, it is worth to point out that the cost-effectiveness conclusion in this population varies when different assumptions on treatment duration of TNFis versus non-TNFis are applied in the model. This assumption impacts to a less extent the conclusions for Populations B and C, where RIT was introduced as a common follow-up therapy, rather than a comparator to CZP as it is the case in Population A. The ERG assumption of longer treatment duration after response with RIT (mean 11.31 years versus 4.06 years for TNFis) lacks clinical plausibility as it was taken from the long-term extension of the REFLEX trial and is highly unlikely to reflect the average duration of therapy in real life clinical practice, as it is well established that patients tend to stay on therapy longer in clinical studies due to the standard of care received and due to access challenges in some regions. This is why in the UCB submission real world data from registries was used to support the assumptions pertaining to duration on therapy. Furthermore, the ERG assumption based on the REFLEX study is also inconsistent with assumptions made by the ERG in TA375, where it was argued that discontinuation rates are dependent on the response status, and not on treatment. As the EULAR rates are marginally more favourable for CZP than RIT, based on the ERG preferred NMA including J-RAPID, this would lead to longer time on treatment for CZP than for RIT. As such the equal treatment duration assumption adopted in the UCB submitted base case would be considered as a more conservative approach, as it potentially underestimates the CZP treatment duration and favours RIT over CZP. UCB would also like to draw the committee's attention to the latest evidence on biologic treatment duration (Ramiro et al 2015),[8] also referenced in the UCB submission. In contrast to the ERG assumptions, the Ramiro et al study, based on the US National Data Bank for Rheumatic Diseases (NDB) registry shows that the discontinuation rate was lower in patients treated with TNFis compared	and closer to the accepted retreatment interval in TA375. See section 4.12 of FAD. Comment noted. The committee acknowledged that treatment duration for TNF inhibitors and non-TNF inhibitors was a key driver for the model. However, the committee was not persuaded by the reasoning that contradictory durations from Ramiro and Du Pan studies should be the basis for assuming equal treatment duration for TNF inhibitors and non-TNF Inhibitors. The committee did acknowledge that there may be bias in using data for a trial to inform the durations but this was still more preferable than assuming equal treatment durations. As such the committee concluded the use of durations from TA195 was acceptable. See section 4.13 of FAD.

Consultee	Comment [sic]	Response
	to non-TNFis when these are used as second line biologics. The contradictory evidence on biologic treatment duration identified from the literature supports that the equal treatment duration assumption is a conservative approach as done in the UCB submitted base case.	
UCB Pharma	**4. Prescribing of biosimilars** In section 4.5 (page 9) of the ACD, the committee states that "*the consensus among rheumatologists is that the etanercept biosimilar should be used in preference to the branded form because it has lower acquisition costs*". UCB would like to note that this statement is not in line with the BSR's position statement on biosimilar use published on their website,[10] which states that BSR "*does not support a universal mandate that all patients should start a biosimilar purely to save costs*". It furthermore states: "*Clinical effectiveness and patient safety should be the overriding principles for prescribing any biological agent. Prescribing should be made on a case by case basis, based on clinical reasons and not solely as a measure to save money*." Accordingly, we feel that the above statement from the ACD does not accurately reflect the BSR position statement on use of the biosimilars and thus request removal of the above mentioned statement in section 4.5.	Comment noted. The views of clinical experts and patient/career representatives, expressed in public, were considered by the Appraisal Committee when formulating its recommendations. See section 4.5 of FAD.
UCB Pharma	**5. CZP Label Information** In Section 2, page 5 of the ACD, the details describing marketing authorisation and other related information should align with the latest summary of product characteristics (SmPC) for CZP.[11] We request revisions of the relevant statement as follows (see underlined text): **Section 2 (page 5):** • Current statement: "*Certolizumab pegol has a marketing authorisation in the UK for the treatment of 'moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs) including MTX*	Comment noted. NICE recognises that the first requested amendment does not accurately reflect the indications for the technology used in this appraisal. The wording has been amended to reflect the following two points. See section 2 of FAD.

Consultee	Comment [sic]	Response
	(methotrexate), has been inadequate'. Certolizumab pegol can be used 'as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate' (see the summary of product characteristics)." Requested revision: "*Certolizumab pegol in combination with methotrexate (MTX) has a marketing authorisation in the UK for the treatment of 'moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs) including MTX, has been inadequate'. Certolizumab pegol can be used 'as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate'. Certolizumab pegol can also be used in combination with MTX for 'the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs' (see the summary of product characteristics)."* • Current statement: "*Certolizumab pegol is associated with common bacterial and viral infections and eosinophilic and leukopenia disorders. More uncommon infections that may limit its use include tuberculosis and sepsis. For full details of adverse reactions and contraindications, see the summary of product characteristics.*" Requested revision: "*Certolizumab pegol is contraindicated in people with active tuberculosis or other severe infections, and in people with moderate or severe heart failure. The summary of product characteristics lists no adverse reactions as very common but notes that in clinical trials the most common adverse reactions were bacterial and viral infections. For full details of adverse reactions and contraindications, see the summary of product characteristics*." • Current statement: "*Loading doses of 400 mg at weeks 0, 2 and 4; maintenance doses of 200 mg every 2 weeks or 400 mg every 4 weeks, once clinical response is confirmed*." Requested revision: "*The recommended starting dose of certolizumab pegol for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. After the starting dose, the recommended maintenance dose of certolizumab pegol is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. MTX should be continued during treatment with certolizumab pegol where appropriate."*	
UCB Pharma	**6. Certolizumab pegol price and Patient Access Scheme**	The FAD has been amended to reflect this - see FAD section 1.1, 2 and

Consultee	Comment [sic]	Response
	In section 1.1 (page 3) of the ACD, it is stated that CZP may only be recommended "*only if the company provides certolizumab pegol with the discount agreed in the patient access scheme*" . As per the agreed scheme with the Department of Health, we would like to clarify that the patient access scheme (PAS) for CZP is not a discount but a scheme by which the first 12 weeks of therapy (currently 10 pre-loaded syringes of 200 mg each) with CZP are free of charge. We therefore would request that the CZP PAS is not referred to a discount, which inaccurately implies that a cost reduction is offered per dose. We would request aligning the wording describing the CZP PAS with what has been agreed with the Department of Health and already reported in recent NICE guidance, including NICE TA375 and TA383	summary
UCB Pharma	**7. Evidence of additional benefits with CZP beyond the QALY** Additional health-related benefits that are not captured by QALY calculations were included in the UCB submission, being outlined in Section 2.5. In particular, the effect of CZP on workplace and household productivity in patients with prior TNFi exposure was described in section 4.7.3.2.4 (pages 108–110) of the UCB submission. Data from the PREDICT study indicated large improvements in workplace and household productivity as well as participation in social activities following CZP treatment. Patients with prior TNFi exposure reported reductions in absenteeism and presenteeism, as well as levels of arthritis interference with work productivity by Week 12, which were maintained long-term to Week 52 following CZP treatment. Similarly, rapid improvements in household productivity and participation in social activities were seen and further maintained to Week 52. These societal benefits have a large benefit to the lives of patients, their family and carers, and the wider economy, but the utility of these benefits were not considered as part of the calculations of the QALYs gained by patients receiving CZP.	Comment noted. The committee concluded that all relevant benefits and costs were adequately captured by the QALY calculation. See section 4.14 of FAD.

Consultee	Comment [sic]	Response
	Similarly, a number of other benefits, which were not captured in the QALY calculation, were outlined in Section 2.5 of the original submission, which were also mentioned by other independent sources: • The unique molecular structure of CZP was mentioned in Section 2.5.1 of the original submission, and subsequently in the NRAS submission in Appendix G (page 5; page 410 of the ACD committee papers). • The administration benefits of CZP were highlighted in Section 2.5.2 of the original submission, and again in the NRAS submission in Appendix G (page 9; page 414 of the ACD committee papers): "[…] Additionally, during the Appraisal Committee meeting on 15th June 2016, the expert rheumatologist of the panel referred to the current off-label evidence of CZP during pregnancy, which has been summarized in the NICE-accredited BSR and BHPR recent guideline on prescribing drugs in pregnancy and breastfeeding: "*Certolizumab pegol is compatible with all three trimesters of pregnancy and has reduced placental transfer compared with other TNF inhibitors (TNFis)*".[13] Certolizumab pegol is not recommended in pregnancy as per its label.[11]	
UCB Pharma	**8. Patients already undergoing treatment with CZP** In section 1.6 of the ACD (page 4), it is stated that "*This guidance is not intended to affect the position of patients whose 1.6treatment with certolizumab pegol was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop*." Whilst we agree with this recommendation, for reasons of clarity and consistency, we would request that this text is aligned with the guidance given for other biologics in the same indication, for example, the equivalent wording used in the latest NICE TA375 guidance:	Comment noted. NICE guidance is prospective. NICE recognises that people may have access to treatments before the marketing authorisation is granted, or before NICE guidance is issued. NICE technology appraisal guidance makes allowances for people who have accessed new treatments before its formal guidance is release. See section 1.4 of FAD.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
British Society of Rheumatology	We would however like to draw to the committee's attention an inconsistency between the treatment threshold in TA 195 and the current ACD. The current draft guidance states clearly that '*certolizumab pegol, in combination with methotrexate, is recommended... only if disease is severe, that is, a disease activity score (DAS28) greater than 5.1*…' However, TA 195, which is addressing the same patient population (i.e. treatment with bDMARDs after failure of one TNFi) states '*Adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are recommended as treatment options only for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab….'.* TA 195 does not insist that such patients have a DAS28 >5.1 at the pint of changing treatment. In clinical practice, treatment non-response is defined as either primary non-response (a patient fails to respond to a bDMARD at/before 6 months) or secondary non-response (patients lose treatment response after initially responding). In all previous NICE TAs of bDMARDS in RA, non-response is defined as not achieving and/or not maintaining a fall in DAS28 of >1.2, from a pre-treatment DAS28 of >5.1. In both primary and secondary non-response, therefore, the DAS28 may be <5.1 at the time of concluding a patient is not responding to their bDMARD. However, in both described cases patients still have severe active RA as their DAS28 before their first bDMARD must have been >5.1. We therefore ask the committee to ensure the terminology surrounding treatment eligibility to be consistent across the technology appraisals that affect patients	Comment noted. The committee considered the request from British Society Rheumatology and clarified its understanding of previous guidance in TA375 and TA195. It understood that both pieces of guidance explicitly state that a first and second biologic should be started if disease is severe. However the committee considered preceding guidance in and parity with existing guidance at the same point in the pathway. The committee concluded that although no evidence was submitted by the company to support use in a moderate population, guidance to initiate a second biologic should not be limited to a DAS28 score as there are other measures of disease activity that may be used in practice. See section 4.2 and 4.4 of FAD.

Nominating organisation	Comment [sic]	Response
	treatment after failure of their first bDMARD, and remove the threshold of DAS28 >5.1 from the current guidance.	

Comments received from commentators

Commentator	Comment [sic]	Response
Merck, Sharp & Dohme	"NICE technology appraisal guidance for adalimumab, etanercept, infliximab, rituximab and abatacept for rheumatoid arthritis recommends rituximab plus methotrexate after inadequate response to, or intolerance to, other DMARDs, including at least 1 TNF-alpha inhibitor. The committee was aware that the guidance provides alternative options where either rituximab or methotrexate is contraindicated or withdrawn " This statement only mentions the 5 TNF-α Inhibitors appraised in NICE Technology Appraisal 195 as alternative options for treating rheumatoid arthritis where either rituximab or methotrexate is contractindicated or withdrawn. This statement does not refer to other NICE Technology Appraisals for golimumab (TA225) and other treatments for the same indication. These NICE recommendations should be mentioned for the purpose of completion.	The FAD has been amended to reflect this - see FAD section 4.1 and 4.2.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF inhibitor: A Single Technology Appraisal [ID824]

July 2016

UCB Response to the Appraisal Consultation Document

Please note that 'academic in confidence' information has been highlighted.

UCB welcomes the opportunity to respond to the appraisal consultation document (ACD) from the first Committee meeting for the single technology appraisal on certolizumab pegol (CZP) for treating rheumatoid arthritis after inadequate response to a TNF inhibitor (TNFi). UCB welcomes the guidance formulated in the ACD, that CZP is a cost-effective option as combination therapy with methotrexate (MTX) or monotherapy, in populations where currently other TNFis are recommended by NICE, that is in adults for whom rituximab (RIT) is contraindicated or not tolerated.

Following a review of the ACD we would like to provide a number of comments and observations for consideration by the NICE committee. These comments are structured into two sections:

(1) Comments related to the UCB submitted evidence, such as the evidence for moderate to severe disease, the network meta-analysis (NMA) and the cost-effectiveness estimates for Population A, including further supportive results;
(2) General comments to the ACD, including factual accuracy, such as the CZP approved Patient Access Scheme (PAS), SmPC., additional benefits beyond the QALY.

Comments related to the UCB submitted evidence

1. Use of certolizumab pegol in patients with moderate to severe disease activity

In section 1.1 (page 3) of the ACD, the committee makes the recommendation for certolizumab pegol to be used in patients with prior failure of a TNFi "*only if disease is severe*". Such wording is also used in other places of the ACD in sections 4.4 and 4.8, as well as in the summary of the committee's conclusions.

UCB would like to note that as per the final scope of the current appraisal set by NICE, the population in which CZP is reviewed is patients with moderate to severe disease activity, which reflects the current marketing authorisation for CZP and is in line with the data submitted and the discussions during the scoping process. Furthermore, as indicated during the scoping workshop by the BSR representative, the eligibility criteria of "severe disease activity" only applies to the initiation of the first biologic, but not to the initiation of a second biologic in patients with inadequate response to the first TNFi.

As per the latest NICE guidance TA375 and the NICE RA pathway,[1, 2] patients who do not have an EULAR moderate response to the initial treatment within 6 months, continue to a second biologic. This is in line with the current BSR guidelines, which similarly indicates that the initial biologic therapy should be withdrawn if an adequate response is not seen despite 6 months of continuous treatment, where adequate response is defined as good or moderate EULAR response.[3]

The latest EULAR recommendation in terms of use of a second TNFi after inadequate response to the first TNFi therapy,[4] which is an established clinical practice, does not indicate any restriction to the disease activity prior to the initiation of the second TNFi.

In order for a patient to be in severe disease activity after at least 6 months of the first TNFi, initiated as per the eligibility criteria indicated in TA375, the patient should have been in a highly severe/refractory disease activity at the time of starting the first biologic therapy. As such, a patient with severe disease activity who received a first TNFi and did not adequately respond to such treatment (due to failure to achieve or maintain a EULAR moderate response), may present with a DAS28<5.1 at the point of assessment of response of the first TNFi, and thus be in moderate disease activity. Consequently, such a patient, although showing inadequate response to a first biologic, would not be eligible for a second TNFi according to the proposed recommendation.

In line with the final decision scope of the NICE appraisal and marketing authorisation for CZP, the UCB submission was based on evidence in adults with moderate to severe, active rheumatoid arthritis (RA) whose disease had not responded adequately to a TNFi. Given that the clinical benefits and cost-effectiveness of CZP presented in the UCB submission and in the ERG's independent analysis reflect the value of CZP across patients of moderate to severe disease activity, we would like to request revision of the recommendation to be aligned to the patient population that the submitted evidence supports, that is, patients with moderate to severe, active RA whose disease has not responded adequately to a TNFi.

Aligned with this request, we would like to highlight all instances where such wording is mentioned in the ACD and request the following revisions (text underlined):

Section 1.1 (page 3) and Section 4 summary (page 13):

- ***Current statement**:* "*Certolizumab pegol, […], is recommended […] only if: disease is severe, that is, a disease activity score (DAS28) greater than 5.1*".
- ***Requested revision:*** "*Certolizumab pegol, […], is recommended […] only if: disease is moderate to severe, that is, a disease activity score (DAS28) greater than 3.2*".

Section 4.4 (page 8):

- ***Current statement**:* "[…] *the company presented treatment sequences for the defined populations, which reflected the clinical pathway for people with severe active rheumatoid arthritis*, […]".
- ***Requested revision:*** "[…] *the company presented treatment sequences for the defined populations, which reflected the clinical pathway for people with moderate to severe active rheumatoid arthritis,* […]".

Section 4.8 (page 10):

- ***Current statement**:* The committee states that they "*saw no evidence to support the use of certolizumab pegol in people who have moderate disease*."
- ***Requested revision:*** As separate evidence for the patient population of moderate disease activity alone does not fall within the scope of this appraisal, we request the removal of this sentence from the ACD.

2. Heterogeneity of the submitted NMA

In section 4.7 (page 9) of the ACD, the committee states that "*Heterogeneity was not appropriately accounted for. This could lead to an over-estimation of effect, favouring certolizumab pegol. The committee heard that the evidence review group (ERG) would have preferred to see random effects models throughout, rather than fixed effects models, because these can adequately capture the heterogeneity expected from the studies included in the analysis*".

UCB respectfully disagrees with the statement implying that the use of a fixed effects model in the UCB network meta-analyses would lead to an over-estimation of the effect of certolizumab pegol, as this statement is unproven and not representative of the ERG's critique of the analyses, which states that the results may not *"represent genuine uncertainty"* (ERG report, page 15). To our knowledge, the ERG report does not explicitly state that the fixed effects model would yield an over-estimation of the effect of certolizumab pegol, in support of the ACD statement.

As indicated in the UCB response to the ERG clarification questions (page 17) as well as the UCB submission (section 5.3.1.5, page 189), a random effects model was not considered in the base case analysis due to the limited number of studies in the network (five studies in the base case, each reporting outcomes comparing a different bDMARD versus PBO). Under such circumstance, the 'weakly informative prior information' suggested by ERG is not applicable. To provide a genuine estimate of between study variance, it may be necessary to use a strongly informative prior for this parameter in the NMA model, and any misspecification of the prior may bias the outcomes of the NMA. Hence, a fixed effects model was preferred to a random effects model in the base case in the UCB submission

To support our point, UCB has performed a random effects meta-analysis using the multinomial likelihood model, and compared the results against the fixed effects model presented in the original UCB submission, in section 5.3.1.5. As shown in Table 1, the mean effect sizes generated from the random effects model (results presented based on the random effect mean and not the mean of the predictive distribution) are equal to the original fixed effect analyses up to and including the second decimal place. The results mainly differ in terms of the 95% credible interval, with the random effects interval greatly exceeding the interval estimated using fixed effects. This is driven by the vague prior distribution assigned to the between study heterogeneity parameter; an issue that is highlighted in the ERG report:

"*When there are insufficient sample data with which to update prior distributions, the prior information will be influential and not uninformative. In such situations, if the prior information does not represent reasonable prior beliefs, then the results will not represent reasonable posterior beliefs"* (section 4.3 – critique of the indirect comparison and/or multiple treatment comparison).

Whilst we agree that there is heterogeneity between the studies, we note that there is currently insufficient information to quantify this heterogeneity and to provide meaningful estimates of

uncertainty in a random effects model (without strongly informative priors). UCB agree with the ERGs assessment that the fixed effects analysis will yield an under-estimation of the uncertainty surrounding the effect of certolizumab pegol, but also note that the random effects model would over-estimate this uncertainty. This is further described in the Cochrane handbook for meta-analysis: "when there is little information, either because there are few studies or if the studies are small, a random-effects analysis will provide poor estimates of the width of the distribution of intervention effects".[5] At present, UCB does not consider the current wording of the ACD to accurately reflect the challenges presented by the submitted meta-analysis, or the ERGs critique.

Accordingly, we would like to request rewording of the statement named above, to more appropriately reflect the UCB evidence and the statements in the ERG report, as well as the additional evidence presented in this document. We would suggest the text to read the following (revisions underlined):

"Heterogeneity was not accounted for; however, it is recognised that there is insufficient information to properly quantify it. This could lead to an under-estimation of the uncertainty surrounding the effectiveness of certolizumab pegol. The committee heard that the evidence review group (ERG) would have preferred to see random effects models throughout, rather than fixed effects models, because these can adequately capture the heterogeneity expected from the studies included in the analysis".

Table 1: Results of network meta-analysis when using a multinomial likelihood function for the EULAR response (fixed effects model from the original submission and new analysis using the random effects model)

Comparison	Mean	L95% CI	U95% CI
Original UCB submission (**fixed effects model**)*			
RIT + MTX vs. PBO + MTX	[redacted]	[redacted]	[redacted]
TOC 8mg + MTX vs. PBO + MTX	[redacted]	[redacted]	[redacted]
TOC 4mg + MTX vs. PBO + MTX	[redacted]	[redacted]	[redacted]
ABT + MTX vs. PBO + MTX	[redacted]	[redacted]	[redacted]
GOL 50 + MTX vs. PBO + MTX	[redacted]	[redacted]	[redacted]
GOL 100 + MTX vs. PBO + MTX	[redacted]	[redacted]	[redacted]
CZP + MTX vs. PBO + MTX	[redacted]	[redacted]	[redacted]
New analysis (**random effects model** with vague prior for between study heterogeneity parameter (uniform distribution with limits of 0 and 2)**			
RIT + MTX vs. PBO + MTX	[redacted]	[redacted]	[redacted]
TOC 8mg + MTX vs. PBO + MTX	[redacted]	[redacted]	[redacted]
TOC 4mg + MTX vs. PBO + MTX	[redacted]	[redacted]	[redacted]
ABT + MTX vs. PBO + MTX	[redacted]	[redacted]	[redacted]
GOL 50 + MTX vs. PBO + MTX	[redacted]	[redacted]	[redacted]
GOL 100 + MTX vs. PBO + MTX	[redacted]	[redacted]	[redacted]
CZP + MTX vs. PBO + MTX	[redacted]	[redacted]	[redacted]

CI=confidence interval; L95%=lower limit of the 95% CI; U95% = upper limit of the 95% CI.
* Treatment effect on the probit scale biologic + MTX versus PBO + MTX (negative value indicates comparator is more efficacious than placebo)
** Results presented based on random effect mean and not the mean of the predictive distribution

3. Cost-effectiveness of certolizumab pegol in Population A

- In section 4.12 (page 12) of the ACD, the committee states that it "*considered the ERG exploratory analyses that included 2 additional sequences in which certolizumab pegol plus methotrexate was placed after, and instead of, rituximab plus methotrexate. The committee considered that these were appropriate sequences to include*".
  Furthermore, in the summary of the ACD section 4 (page 18) of the ACD, the committee discusses key drivers of cost effectiveness, stating that it "*paid particular attention to the treatment sequence used by the company for the population for whom rituximab plus methotrexate is a treatment option and noted that placing certolizumab pegol plus methotrexate before rituximab plus methotrexate was not a valid comparison as it did not replace it*."

Lastly, in the summary of the ACD section 4 (page 19), the committee states that it "*concluded that the most likely ICER for people for whom rituximab plus methotrexate is a treatment option was above the normal range that would be considered a cost effective use of NHS resources*".

As outlined in the UCB response to ERG clarification question B.2 (page 30 of the UCB response), the sequence of therapies considered for population A were selected based on the expert opinion of a clinical rheumatologist, with experience in treating RA patients in clinical practice in England. The clinical expert opinion was that it would be clinically reasonable to consider certolizumab pegol (CZP) before RIT, unless contraindicated, to allow a second TNFi treatment option, before switching to another mechanism of action agent. The sequence CZP placed after RIT (where TOC + MTX is currently placed according to TA247) in Population A was considered not to be relevant to the final scope of this appraisal, and thus not included in the UCB submission. UCB recognise that one of the additional ERG scenarios of CZP instead of RIT is a relevant strategy and should therefore be explored as part of the economic analyses.

UCB has conducted new analyses on the 3 relevant sequences (CZP before RIT, CZP instead of RIT and RIT) using the revised ERG model. The following changes in ERG model inputs and assumptions were made, to reflect those used in the UCB submitted basecase cost-effectiveness analysis:

- Treatment discontinuation: the rate of discontinuation for RIT and TOC equals the CZP discontinuation rate of 11.6% (executable model: Duration of therapy$M20:M23 = 11.6%, and Duration of therapy$DUR_SEQ2 = Duration of therapy$DUR_SEQ1)
- Initial HAQ change for palliative care: an error seems to have been introduced during the revisions made by the ERG to the UCB latest submitted executable model; the initial change should equal 0, as per the UCB submission (page 199) (executable model correction: Model parameters$G64 = 0)
- RIT retreatment: a six monthly re-treatment for RIT was assumed (executable model: Datastore$G31=2)

The conservative assumption of equal treatment discontinuation rate was maintained as in the UCB submitted basecase, based on the ERG assumptions adopted in the NICE TA375,[1] as well as given the contradictory evidence on treatment duration of TNFis versus non-TNFis identified in the literature, which is further discussed below. The second assumption on the RIT retreatment cycle length of 6 months was also maintained as in the UCB submitted basecase, as supported by the SmPC and the NICE TA195[6] guidance for RIT. Further sensitivity analyses were conducted for these two assumptions and are provided below.

All other assumptions, eg. TOC as the only follow up biologic in the sequence, mortality dependent on baseline HAQ only, and data inputs remained the same as in the revised ERG model (ERG report, page 149). The result of the new analysis is presented in Table 2 below (deterministic results).

The results indicated that the least effective strategy in the analysis was the RIT sequence, followed by CZP instead of RIT and CZP before RIT as the most effective.

CZP is associated with a higher response rate versus RIT according to the submitted NMA including J-RAPID (ERG preferred base case), resulting in a marginally higher QALY gain for CZP vs RIT (incremental QALY of +0.03). The CZP instead of RIT sequence was slightly costlier over lifetime (£3,467) than RIT sequence, with an associated ICER of £130,382, given the marginally incremental QALYs observed.

The CZP before RIT sequence was the most effective and costliest strategy. The increase in cost and QALYs are due to the additional line of biologic therapy permitted in the CZP before RIT sequence (3 biologics), when compared to CZP instead of RIT and RIT sequences which included only 2 biologics. The incremental QALYs and costs of the CZP before RIT over the RIT sequence were of +0.42 QALY and £10,763 over lifetime, with an associated ICER of £25,682 per QALY gained.

Table 2: Population A: additional cost effectiveness deterministic results

Sequences	Total cost	Total QALY	Incremental cost	Incremental QALY	ICER versus reference
RIT + MTX*	£119,814	7.266	-	-	
CZP+MTX instead of RIT+MTX	£123,281	7.293	£3,467	0.03	£130,382
CZP+MTX before RIT+MTX*	£130,577	7.685	£10,763	0.42	£25,682

* Assumes 6 monthly treatment for RIT

One of the key drivers of the cost-effectiveness analysis is the assumption related to the biologic treatment duration after initial response, as indicated by the sensitivity analyses included in the UCB submission (pages 245 and 249). More specifically for Population A, it is worth to point out that the cost-effectiveness conclusion in this population varies when different assumptions on treatment duration of TNFis versus non-TNFis are applied in the model (see Tables 3-5 below). This assumption impacts to a less extent the conclusions for Populations B and C, where RIT was introduced as a common follow-up therapy, rather than a comparator to CZP as it is the case in Population A.

A summary of the assumptions on discontinuation rates/treatment duration made in the UCB submission and those referenced by the ERG is provided in Table 3 below.

Table 3: Summary of assumptions on discontinuation rates/ treatment duration of biologic therapies

	Assumption	Values on treatment duration/ discontinuation rate	Source
UCB submission	*Base case:* Discontinuation rate same for all biologic treatments	6 month discontinuation rate: 15.6%	BSRBR[7]
	Sensitivity analysis: Discontinuation rate lower with TNF*	Annual discontinuation rate: - TNFi: 19% - Non-TNFi: 38%	Ramiro 2015 (NDB registry)[8]
	Sensitivity analysis: Duration on treatment longer with non-TNF**	Median duration: - TNFi : 21 months (IQR 7-53) - Non-TNFi: 31 months (IQR 13-63)	Du Pan 2012[9]
ERG report / TA195	Discontinuation rate higher with TNF	Mean duration: - TNFi: 4.06 years - Rituximab: 11. 31 years - Abatacept: 6.17 years 6-month discontinuation rate : - TNFi: 11.6% - Rituximab: 4.3% - Abatacept/ tocilizumab: 7.8%	REFLEX long-term extension BMS submission BSRBR[6]

*unadjusted HR 0.64 (0.48 to 0.84), adjusted HR 0.68 (0.51 to 0.90) for TNFi vs non-TNFi; Using shape=1 (exponential) and scale=0.19 for TNFi and scale=0.38 for non-TNFi (e.g. discontinuation rate greater for non-TNFis versus TNFis)
**crude HR 0.75 (0.63 to 0.89), adjusted HR 0.50 (0.41 to 0.62) for non-TNFi vs TNFi; Scale parameter for Weibull distribution: TNFi: 0.4414; non-TNFi: 0.2207

The ERG assumption of longer treatment duration after response with RIT (mean 11.31 years versus 4.06 years for TNFis) lacks clinical plausibility as it was taken from the long-term extension of the REFLEX trial and is highly unlikely to reflect the average duration of therapy in real life clinical practice, as it is well established that patients tend to stay on therapy longer in clinical studies due to the standard of care received and due to access challenges in some regions. This is why in the UCB submission real world data from registries was used to support the assumptions pertaining to duration on therapy. Furthermore, the ERG assumption based on the REFLEX study is also inconsistent with assumptions made by the ERG in TA375, where it was argued that discontinuation rates are dependent on the response status, and not on treatment. As the EULAR rates are marginally more

favourable for CZP than RIT, based on the ERG preferred NMA including J-RAPID, this would lead to longer time on treatment for CZP than for RIT. As such the equal treatment duration assumption adopted in the UCB submitted base case would be considered as a more conservative approach, as it potentially underestimates the CZP treatment duration and favours RIT over CZP.

UCB would also like to draw the committee's attention to the latest evidence on biologic treatment duration (Ramiro et al 2015),[8] also referenced in the UCB submission. In contrast to the ERG assumptions, the Ramiro et al study, based on the US National Data Bank for Rheumatic Diseases (NDB) registry shows that the discontinuation rate was lower in patients treated with TNFis compared to non-TNFis when these are used as second line biologics.

The contradictory evidence on biologic treatment duration identified from the literature, as indicated in Table 3, supports that the equal treatment duration assumption is a conservative approach as done in the UCB submitted base case. Further sensitivity analysis was performed to the above new cost-effectiveness analysis, with varied assumptions on treatment duration of biologic treatments. The discontinuation rates for the first and subsequent biologic treatments in TNFi-IR patients were based on Ramiro et al. 2015 (higher discontinuation rate/shorter treatment duration for non-TNFi compared to TNFi) and Du Pan et al. 2012 (lower discontinuation rate/longer treatment duration for non-TNFi compared to TNFi) as indicated in the UCB submission.[8, 9]

The results of the additional sensitivity analyses on treatment discontinuation are presented in Tables 4 and 5.

When assuming a greater discontinuation rate (ie shorter treatment duration) for non-TNFi (RIT and TOC) compared to TNFis (Table 4), the sensitivity analysis yields favourable results for both CZP sequences, when CZP is given either instead of or before RIT. The analysis indicates that CZP instead of RIT is cost-effective at a willingness-to-pay (WTP) threshold of £16,230 (vs RIT). On the other hand, when assuming a smaller discontinuation rate (ie longer treatment duration) for non-TNFis (RIT and TOC) compared to TNFi, the results favour the RIT sequence (Table 5). Under this assumption, RIT becomes the most effective strategy and is cost-effective versus CZP instead of RIT at WTP threshold > £4,968/QALY. CZP before RIT is dominated by RIT (more costly and less effective).

Table 4: Population A: results of the sensitivity analysis assuming a greater discontinuation rate for non-TNFi compared to TNFi based on Ramiro et al 2015[8]

Sequences	Total cost	Total QALY	Incremental cost	Incremental QALY	ICER versus reference
RIT + MTX*	£110,247	6.713	-	-	-
CZP+MTX instead of RIT+MTX	£120,689	7.354	£10,442	0.641	£16,230
CZP+MTX before RIT+MTX*	£126,767	7.669	£16,520	0.955	£17,293

Ramiro et al 2015: using shape=1 (exponential) and scale=0.19 for TNFi and scale=0.38 for non-TNFi (eg. greater discontinuation rate for non-TNFis versus TNFis).
* Assumes 6 monthly treatment for RIT.

Table 5: Population A: results of the sensitivity analysis assuming a smaller discontinuation for non-TNFis compared to TNFis based on Du Pan et al 2012[9]

Sequences	Total cost	Total QALY	Incremental cost	Incremental QALY	ICER versus reference	ICER versus RIT+MTX
CZP+MTX instead of RIT+MTX	£134,845	7.557	-	-	-	£4,698
RIT + MTX*	£138,564	8.348	£3,719	0.791	£4,698	-
CZP+MTX before RIT+MTX*	£143,523	8.049	£8,678	0.492	£17,644	Dominated

Du Pan et al. 2012: rate of discontinuation for non-TNFis assumed to be reduced by 50% (ie smaller discontinuation rate for RIT).
* Assumes 6 monthly treatment for RIT.

Another sensitivity analysis was performed assuming re-treatment with RIT every 7.35 months, as per the ERG base case (Table 6), instead of every 6 months. The results of this analysis are largely consistent with the previous base case (Table 2) with CZP instead of RIT extendedly dominated by RIT and CZP before RIT. The ICER of CZP before RIT versus RIT is £30,441 per QALY gained.

Table 6: Population A: results of the sensitivity analysis assuming a course of rituximab given every 7.35 months and the same discontinuation rates for non-TNFi and TNFi.

Sequences	Total cost	Total QALY	Incremental cost	Incremental QALY	ICER versus reference
RIT + MTX*	£115,534	7.266	-	-	-
CZP+MTX instead of RIT+MTX	£123,281	7.293	£7,748	0.03	£291,331
CZP+MTX before RIT+MTX*	£128,279	7.685	£12,746	0.42	£30,411

* Assumes a course of rituximab is given every 7.35 months

Furthermore, when assuming the same 7.35 months retreatment course for RIT, but a greater discontinuation rate (ie shorter treatment duration) for non-TNFis (RIT and TOC) compared to TNFi as in Table 3, the results are consistent with the previous ones yielding favourable results for both CZP sequences, when CZP is given either instead of or before RIT (Table 7).

Table 7: Population A: results of the sensitivity analysis assuming a course of rituximab is given every 7.35 months and a greater discontinuation rate for non-TNFi compared to TNFi based on Ramiro et al 2015[8]

Sequences	Total cost	Total QALY	Incremental cost	Incremental QALY	ICER versus reference
RIT + MTX*	£107,510	6.713	-	-	-
CZP+MTX instead of RIT+MTX	£120,689	7.354	£13,178	0.641	£20,571
CZP+MTX before RIT+MTX*	£125,169	7.669	£17,659	0.955	£18,485

Ramiro et al 2015: using shape=1 (exponential) and scale=0.19 for TNFi and scale=0.38 for non-TNFi (eg. greater discontinuation rate for non-TNFis versus TNFis).
* Assumes a course of rituximab is given every 7.35 months

The new base case and the four sensitivity analyses in Population A above show that the ICER of CZP before RIT compared to RIT ranges mostly between £17,000 and just above the threshold of £30,000 per QALY gained (£30,411), in most of the scenarios presented (four out of five), with the only exception when assuming the discontinuation rates from Du Pan 2012. As pointed out earlier, treatment duration is a key driver of cost-effectiveness in Population A, which drives the ICER of CZP before RIT vs RIT from £17,293 (Table 4) to being dominated (Table 5), while most of the results indicate that the CZP before RIT is a cost-effective treatment option when compared to RIT. Similarly, the above results indicate that the ICER of CZP instead of RIT compared to RIT lies below £20.571 in 3 out of 5 cases, whereas in the other 2 cases, given that CZP instead of RIT sequence was slightly costlier over lifetime than RIT sequence and had a marginally higher QALYs, the ICER is >£100,000.

UCB would like the committee to consider the above-mentioned new analysis indicating that CZP+MTX can be a cost-effective option before or instead of RIT+MTX, taking into account the uncertainty around the assumed duration on biologic treatment.

General comments, including factual accuracy

4. Prescribing of biosimilars

In section 4.5 (page 9) of the ACD, the committee states that "*the consensus among rheumatologists is that the etanercept biosimilar should be used in preference to the branded form because it has lower acquisition costs*".

UCB would like to note that this statement is not in line with the BSR's position statement on biosimilar use published on their website,[10] which states that BSR "*does not support a universal mandate that all patients should start a biosimilar purely to save costs*". It furthermore states: "*Clinical effectiveness and patient safety should be the overriding principles for prescribing any biological agent. Prescribing should be made on a case by case basis, based on clinical reasons and not solely as a measure to save money*."

Accordingly, we feel that the above statement from the ACD does not accurately reflect the BSR position statement on use of the biosimilars and thus request removal of the above mentioned statement in section 4.5.

5. CZP Label Information

In Section 2, page 5 of the ACD, the details describing marketing authorisation and other related information should align with the latest summary of product characteristics (SmPC) for CZP.[11] We request revisions of the relevant statement as follows (see underlined text):

Section 2 (page 5):

- Current statement: "*Certolizumab pegol has a marketing authorisation in the UK for the treatment of 'moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs) including MTX (methotrexate), has been inadequate'. Certolizumab pegol can be used 'as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate' (see the summary of product characteristics).*"

  Requested revision: "*Certolizumab pegol <u>in combination with methotrexate (MTX)</u> has a marketing authorisation in the UK for the treatment of 'moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs) including MTX, has been inadequate'. Certolizumab pegol can be used 'as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate'. <u>Certolizumab pegol can also be used in combination with MTX for 'the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs'</u> (see the summary of product characteristics)."*

- Current statement: "*Certolizumab pegol is associated with common bacterial and viral infections and eosinophilic and leukopenia disorders. More uncommon infections that may limit its use include tuberculosis and sepsis. For full details of adverse reactions and contraindications, see the summary of product characteristics.*"

  Requested revision: "*Certolizumab pegol is <u>contraindicated in people with active tuberculosis or other severe infections, and in people with moderate or severe heart failure. The summary of product characteristics lists no adverse reactions as very common but notes that in clinical trials the most common adverse reactions were bacterial and viral infections.</u> For full details of adverse reactions and contraindications, see the summary of product characteristics*."

- Current statement: "*Loading doses of 400 mg at weeks 0, 2 and 4; maintenance doses of 200 mg every 2 weeks or 400 mg every 4 weeks, once clinical response is confirmed*."

  Requested revision: "*<u>The recommended starting dose of certolizumab pegol for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. After the starting dose, the recommended maintenance dose of certolizumab pegol is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. MTX should be continued during treatment with certolizumab pegol where appropriate."</u>*

6. Certolizumab pegol price and Patient Access Scheme

In section 1.1 (page 3) of the ACD, it is stated that CZP may only be recommended "*only if the company provides certolizumab pegol with the discount agreed in the patient access scheme*".

As per the agreed scheme with the Department of Health, we would like to clarify that the patient access scheme (PAS) for CZP is not a discount but a scheme by which the first 12 weeks of therapy (currently 10 pre-loaded syringes of 200 mg each) with CZP are free of charge.

We therefore would request that the CZP PAS is not referred to a discount, which inaccurately implies that a cost reduction is offered per dose. We would request aligning the wording describing the CZP PAS with what has been agreed with the Department of Health and already reported in recent NICE guidance, including NICE TA375 and TA383.[1, 12] We have outlined all cases of wording relating to the cost and PAS and the requested revisions as follows (see underlined text):

Section 1.1 (page 3):

- Current statement*:* "*The company provides certolizumab pegol with the discount agreed in the patient access scheme"*
  Requested revision*:* "*The company provides certolizumab pegol as agreed in the patient access scheme"*

Section 2 (page 5):

- Current statement: *"£715.00 per 2-syringe pack"*
  Requested revision: "*The net price of certolizumab pegol is £357.50 per 200-mg prefilled syringe"*

- Current statement: "*This scheme provides a discount where the first 12 weeks of treatment is provided free of charge for certolizumab pegol which is equivalent to 10 vials"*
  Requested revision: *"In the scheme, the first 12 weeks of therapy (currently 10 pre-loaded syringes of 200 mg each) with certolizumab pegol are free of charge"*

Summary (page 14):

- Current statement: *"and the company provides certolizumab pegol with the discount agreed in the patient access scheme"*
  Requested revision: "*and the company provides certolizumab pegol as agreed in the patient access scheme"*

7. Evidence of additional benefits with CZP beyond the QALY

In the summary of the ACD section 4 (page 14 and 18), the committee states that "*no evidence was presented to suggest that there are additional innovative benefits that have not already been captured in the estimate of the QALY*" and "*no other health-related benefits have been identified that have not been captured in the QALY calculation*", respectively. UCB would like to note that this statement does not accurately reflect the evidence submitted and some points raised during the Appraisal Consultation meeting, which describe benefits of CZP that were not captured in the estimations of the QALYs gained.

Additional health-related benefits that are not captured by QALY calculations were included in the UCB submission, being outlined in Section 2.5.

In particular, the effect of CZP on workplace and household productivity in patients with prior TNFi exposure was described in section 4.7.3.2.4 (pages 108–110) of the UCB submission. Data from the PREDICT study indicated large improvements in workplace and household productivity as well as participation in social activities following CZP treatment. Patients with prior TNFi exposure reported reductions in absenteeism and presenteeism, as well as levels of arthritis interference with work productivity by Week 12, which were maintained long-term to Week 52 following CZP treatment. Similarly, rapid improvements in household productivity and participation in social activities were seen and further maintained to Week 52. These societal benefits have a large benefit to the lives of patients, their family and carers, and the wider economy, but the utility of these benefits were not considered as part of the calculations of the QALYs gained by patients receiving CZP.

Similarly, a number of other benefits, which were not captured in the QALY calculation, were outlined in Section 2.5 of the original submission, which were also mentioned by other independent sources:

- The unique molecular structure of CZP was mentioned in Section 2.5.1 of the original submission, and subsequently in the NRAS submission in Appendix G (page 5; page 410 of the ACD committee papers).

- The administration benefits of CZP were highlighted in Section 2.5.2 of the original submission, and again in the NRAS submission in Appendix G (page 9; page 414 of the ACD committee papers): "[…]

Additionally, during the Appraisal Committee meeting on 15th June 2016, the expert rheumatologist of the panel referred to the current off-label evidence of CZP during pregnancy, which has been summarized in the NICE-accredited BSR and BHPR recent guideline on prescribing drugs in pregnancy and breastfeeding: "*Certolizumab pegol is compatible with all three trimesters of pregnancy and has reduced placental transfer compared with other TNF inhibitors (TNFis)*".[13] Certolizumab pegol is not recommended in pregnancy as per its label.[11]

We have outlined all cases of wording relating to evidence of additional benefits and our suggestions for revision (underlined text) below**,** to accurately reflect the evidence submitted by UCB:

Summary (page 14):

- Current statement: *"No evidence was presented to suggest that there are additional innovative benefits that have not already been captured in the estimate of the QALY"*

  Requested revision: *"Evidence was submitted by the manufacturer to support additional innovative benefits for certolizumab pegol including its novel molecular structure as the only PEGylated FAB' fragment TNFi currently available for the treatment of RA and its administration"*

Summary (page 18):

- Current statement: *"No other health-related benefits have been identified that have not been captured in the QALY calculation"*

  Requested revision: "*Other health-related benefits were provided in the manufacture's submission that were not been captured in the QALY calculation, such as improvements in work- and household productivity."*

8. Patients already undergoing treatment with CZP

In section 1.6 of the ACD (page 4), it is stated that "*This guidance is not intended to affect the position of patients whose 1.6treatment with certolizumab pegol was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop*."

Whilst we agree with this recommendation, for reasons of clarity and consistency, we would request that this text is aligned with the guidance given for other biologics in the same indication, for example, the equivalent wording used in the latest NICE TA375 guidance: "*People whose treatment with adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab or abatacept is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop*".

We have outlined the requested revisions as follows (see underlined text):

- Current statement: *"This guidance is not intended to affect the position of patients whose treatment with certolizumab pegol was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop"*

  Requested revision: "*People whose treatment with certolizumab pegol is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop*."

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BSR response to:

Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF inhibitor [ID824]

We are grateful to NICE for providing British Society for Rheumatology the opportunity to comment on the appraisal consultation document (ACD) on the use of certolizumab pegol for treating rheumatoid arthritis (RA) after inadequate response to a TNF inhibitor (TNFi).

Overall, we are supportive with the committee's provisional guidance, and feel the evidence presented is a fair representation of the clinical issues. We would like to re-iterate that patients who do not respond adequately to conventional DMARDs (cDMARDs) and a first TNFi do require a variety of options for their next treatment step, and for many patients a 2nd TNFi is the most suitable option.

Such patients would include those in whom methotrexate and/or rituximab are not tolerated or are contra-indicated, as per the draft guidance. We feel that it is reasonable therefore for certolizumab pegol to be considered at this stage in treatment as an alternative TNFi, as are other TNFi drugs (adalimumab, etanercept, and infliximab) in TA195.

A common example of such a patient, where several therapeutic options enhance clinical care, is a woman planning a pregnancy whilst failing to respond to her initial bDMARD. In this scenario methotrexate is obviously contraindicated, and a 2nd TNFi is a logical next step. There is emerging clinical evidence that certolizumab pegol is a very good option for these women due the low placental transfer of the drug, especially in the first trimester. It is important that patients and their rheumatologists are able to access the drug they feel is most appropriate at each treatment step, and this technology appraisal helps deliver a more personalized approach to medical care.

We would however like to draw to the committee's attention an inconsistency between the treatment threshold in TA 195 and the current ACD. The current draft guidance states clearly that '*certolizumab pegol, in combination with methotrexate, is recommended... only if disease is severe, that is, a disease activity score (DAS28) greater than 5.1*…' .

However, TA 195, which is addressing the same patient population (i.e. treatment with bDMARDs after failure of one TNFi) states '*Adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are recommended as treatment options only for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive*

rituximab….'. TA 195 does not insist that such patients have a DAS28 >5.1 at the pint of changing treatment.

In clinical practice, treatment non-response is defined as either primary non-response (a patient fails to respond to a bDMARD at/before 6 months) or secondary non-response (patients lose treatment response after initially responding). In all previous NICE TAs of bDMARDS in RA, non-response is defined as not achieving and/or not maintaining a fall in DAS28 of >1.2, from a pre-treatment DAS28 of >5.1.

In both primary and secondary non-response, therefore, the DAS28 may be <5.1 at the time of concluding a patient is not responding to their bDMARD. However, in both described cases patients still have severe active RA as their DAS28 before their first bDMARD must have been >5.1.

We therefore ask the committee to ensure the terminology surrounding treatment eligibility to be consistent across the technology appraisals that affect patients treatment after failure of their first bDMARD, and remove the threshold of DAS28 >5.1 from the current guidance.

[redacted]

On behalf of BSR.

Meindert Boysen
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2nd August 2016

Dear Mr Boysen,

RE: APPRAISAL CONSULTATION DOCUMENT: CERTOLIZUMAB PEGOL FOR TREATING RHEUMATOID ARTHRITIS AFTER INADEQUATE RESPONSE TO A TNF INHIBITOR [ID 824]

MSD welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for the NICE Technology Appraisal of certolizumab pegol for treating Rheumatoid Arthritis after inadequate response to a TNF-α Inhibitor.

The following are MSD comments on the ACD and Evidence Review Group Report:

Section	Comments
ACD Section 4.1	"NICE technology appraisal guidance for adalimumab, etanercept, infliximab, rituximab and abatacept for rheumatoid arthritis recommends rituximab plus methotrexate after inadequate response to, or intolerance to, other DMARDs, including at least 1 TNF-alpha inhibitor. The committee was aware that the guidance provides alternative options where either rituximab or methotrexate is contraindicated or withdrawn " This statement only mentions the 5 TNF-α Inhibitors appraised in NICE Technology Appraisal 195 as alternative options for treating rheumatoid arthritis where either rituximab or methotrexate is contractindicated or withdrawn. This statement does not refer to other NICE Technology Appraisals for golimumab (TA225) and other treatments for the same indication. These NICE recommendations should be mentioned for the purpose of completion.
Committee papers, Evidence Review Group Report, page 26	Similar to the ACD statement above, the ERG mentioned treatments included in NICE TA195 and TA274 but did not mention NICE recommendation for golimumab in TA225 as a treatment option in patients for whom rituximab is contraindicated or withdrawn.

Section	Comments
Committee papers, Evidence Review Group Report, Section 5.3.1.2	Whilst evidence from GO-AFTER study was included in the Mixed Treatment Comparison and subsequently in the cost-effectiveness analysis, data from the GO-AFTER extension study[1] were not considered, which reflects significant improvements in long term treatment benefits associated with golimumab treatment compared to the original study. This study extension assessed long-term golimumab therapy in patients with RA who discontinued previous TNF-α inhibitors for any reason. Patients received placebo (Group 1), 50 mg golimumab (Group 2) or 100 mg golimumab (Group 3) subcutaneous injections every 4 weeks. Patients from Groups 1 and 2 with <20% improvement in tender/swollen joints at week 16 early escaped to golimumab 50 mg and 100 mg, respectively. At week 24, Group 1 patients crossed over to golimumab 50 mg, Group 2 continued golimumab 50/100 mg per escape status and Group 3 maintained dosing. Data through week 160 are reported. Four hundred and fifty-nine of the 461 randomised patients were treated; 236/459 (51%) continued treatment through week 160. From week 24 to week 100, ACR20 (≥20% improvement in American College of Rheumatology criteria) response and ≥0.25 unit HAQ (Health Assessment Questionnaire) improvement were sustained in 70-73% and 75-81% of responding patients, respectively. Overall at week 160, 63%, 67% and 57% of patients achieved ACR20 response and 59%, 65% and 64% had HAQ improvement ≥0.25 unit in Groups 1, 2 and 3, respectively. Adjusted for follow-up duration, adverse event incidences (95% CI) per 100 patient-years among patients treated with golimumab 50 mg and 100 mg were 4.70 (2.63 to 7.75) and 8.07 (6.02 to 10.58) for serious infection, 0.95 (0.20 to 2.77) and 2.04 (1.09 to 3.49) for malignancy and 0.00 (0.00 to 0.94) and 0.62 (0.17 to 1.59) for death, respectively. In patients with active RA who discontinued previous TNF-antagonist treatment, golimumab 50 and 100 mg injections every 4 weeks yielded sustained improvements in signs/symptoms and physical function in 57-67% of patients who continued treatment. Golimumab safety was consistent with other anti-TNF agents, although definitive conclusions regarding long-term safety require further monitoring.

[1] Smolen *et al*., Golimumab in patients with active rheumatoid arthritis who have previous experience with tumour necrosis factor inhibitors: results of a long-term extension of the randomised, double-blind, placebo-controlled GO-AFTER study through week 160. Ann Rheum Dis. 2012 Oct;71(10):1671-9.

Section	Comments
Evidence Review Group Report, Table 64, page 172	The ERG presented a table of cost-effectiveness analysis for comparator TNF-α Inhibitors in patient population B (where rituximab is contraindicated or withdrawn). This table was also presented in the committee presentation as a scenario analysis assuming that all TNF-α Inhibitors have the same efficacy as certolizumab. Despite this assumption, the result of the modelling performed by the ERG showed that the total QALYs associated with golimumab treatment is lower than those for etanercept, adalimumab, certolizumab and infliximab, which all produced equal QALYs in the economic model. This is contradicting with the assumption above.

MSD would welcome any comments or questions on the comments made in this letter and look forward to further engagements with NICE on this topic.

Kind regards,

[redacted]

Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF inhibitor: A Single Technology Appraisal

ERG's critique of company's response to the ACD

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Executive Summary

Following the publication of the Appraisal Consultation Document (ACD) the company has provided new analyses for Population A, consisting of patients for whom rituximab (RTX) in combination with methotrexate (MTX) is not contraindicated or has been withdrawn due to an adverse event. The company performed their new analyses based on the amended model produced by the Evidence Review Group (ERG) having applied three additional changes:

- Assuming the same treatment duration for all biologic disease-modifying antirheumatic drugs (bDMARDs)
- Assuming a retreatment interval of 6 months for RTX.
- The company fixed an error in the model, introduced by the ERG in their amended version,that applied an initial improvement in HAQ score to patients on palliative care.

The company presented the results of new analyses including these changes. According to their base case analysis, certolizumab pegol (CZP) in combination with MTX before RTX + MTX is expected to produce an extra 0.42 QALYs at an additional cost of £10,763; this leads to an estimated incremental cost-effectiveness ratio (ICER) of £25,682 per QALY gained. The sequence where CZP + MTX replaced RTX + MTX was extendedly dominated by the other two sequences in the base case. The company also presented the results of scenario analyses using different assumptions for treatment duration and the retreatment interval of RTX. The cost-effectiveness estimates for CZP + MTX before RTX + MTX compared with RTX + MTX ranged from £17,293 per QALY gained to dominated. The results of the scenario analyses for the sequence with CZP + MTX treatment instead of RTX + MTX are discussed below.

The ERG believes that there is stronger evidence to RTX being associated with a longer treatment duration than Tumour Necrosis Factor inhibitors (TNFi). The ERG considers that the evidence presented by the company to the contrary has severe limitations, such as mixing RTX with other non-TNFis and the low number of patients on non-TNFis. After further consideration of the evidence the ERG notes that the retreatment interval for RTX used in the model should be the mean retreatment interval from the REFLEX trial (307 days or 10.09 months), from which the efficacy of RTX + MTX was estimated.

The ERG performed new analyses based on the company's base case incorporating the following changes: setting the retreatment interval for RTX to 307 days; and using the treatment duration estimates for TA195 (the same as those used in the original ERG report). In the ERG's base case, the

currently recommended sequence, RTX + MTX, dominated both CZP + MTX before RTX + MTX and CZP + MTX instead of RTX + MTX. In the ERG's new scenario analyses, the lowest estimated ICER for CZP + MTX before RTX + MTX compared with RTX + MTX was £34,265 per QALY gained. The ERG notes that these analyses do not include the confidential PAS for tocilizumab (TOC): the results of these analyses including the PAS for TOC are included in a confidential appendix.

Finally, the ERG believes that the methodology used within the company's model for evaluating first and subsequent treatments is limited and can result in implausible results when comparing elongated sequences or when the duration of the first treatments in the sequences compared are significantly different to each other. Therefore, the ERG considers that the credibility of comparisons of sequences of different lengths within the model is limited.

Critique of the company's changes to the ERG's amended model

The company applied three changes in the ERG's amended model that affect the analyses: setting the treatment duration of non-TNFis to that of TNFis; setting the retreatment interval of RTX to 6 months, and; fixing an error introduced by the ERG in the amended model which applied an improvement in HAQ score for patients on palliative care. The ERG acknowledges this as an error and notes that it led to the overestimation of the ICER of longer sequences compared with shorter sequences, since fewer patients received palliative care in longer sequences and for a shorter period of time. The other two changes are discussed below.

Equal treatment duration for TNFi-s and RTX

The company's response to the ACD referred to two sources, Ramiro *et al.*[1] and Du Pan *et al.*[2] which report opposite results regarding the relative treatment duration of TNFis compared with non-TNFis, to justify their assumption of equal treatment duration for all bDMARDs. Ramiro *et al.*[1] and Du Pan *et al.*[2] are both observational studies that provide data on the treatment duration of TNFis compared with that of non-TNFis. The ERG notes that the fact that very different drugs such as RTX, TOC and abatacept (ABA) are grouped together might result in an inaccurate estimate of RTX treatment duration.

Table 1 contains a summary of the characteristics of the two studies.

Table 1: Summary of characteristics of Ramiro et al.[1] and Du Pan *et al.*[2]

		Ramiro *et al.*[1]	Du Pan *et al.*[2]
Country		USA	Switzerland
Source of data		National Data Bank for Rheumatic Diseases (NDB)	Swiss rheumatoid arthritis registry (SCQM-RA)
Number of patients	TNFi	988	853
	non-TNFi (% of RTX)	109 (39)	632 (55)
Results		Longer treatment duration on TNFis. Annual discontinuation rate: TNFi: 19% Non-TNFi: 38%	Longer treatment duration on non-TNFis. Discontinuation hazard ratio 0.50 (95% CI 0.41 to 0.62) for non-TNFis compared to TNFis.

The ERG notes that Ramiro *et al.*[1] studied a small number of patients on non-TNFis (109) compared with Du Pan *et al.*[2] (632) and that the percentage of patients on RTX within the non-TNFi group is also smaller in Ramiro *et al.*[1] (39%) than in Du Pan *et al.*[2] (55%). The authors of Ramiro *et al.*[1] acknowledge the "relatively low number of patients on a non-TNFi" as the main limitation of their study. Contradicting previous evidence, Ramiro *et al.*[1] hypothesise that it "may be the case that there are differences between European and American patients, due to different prescription patterns, reimbursement policies, patients' comorbidities, etc." As such, the ERG considers Ramiro *et al.*[1] not to be an appropriate source to estimate the treatment duration.

The company stated that the assumptions on treatment duration used by the ERG were inconsistent with those used by the Assessment Group (AG) in TA375, whereby discontinuation rates were dependent on response status, and not on treatment. The ERG notes that if it had adopted the treatment duration assumptions used in TA375, it then would have been inconsistent with the assumptions made by the AG in TA195. The ERG notes that RTX was one of the drugs assessed in TA195, unlike in TA375, where it was only part of the common treatment sequence. Therefore, the difference in treatment between RTX and other bDMARDs did not impact its relative effectiveness in TA375 as much as it did in TA195 and it does in the current appraisal.

The company also criticised the source of the treatment duration estimates used by the ERG, which was adopted from the economic model built by the AG for TA195.[3] The company claims that the treatment duration used by the ERG has no clinical plausibility because it was based on the open-label extension of the REFLEX trial. The company argues that patients tend to stay on therapy longer in clinical studies and therefore the source used by the ERG is likely to overestimate treatment duration compared with real life clinical practice. The ERG acknowledges the risk of bias but believes TA195

to be the most accurate source for this estimate given that it is the only one that reports treatment duration of RTX, rather than the treatment duration of non-TNFis. The ERG have assessed the impact of this uncertainty in the sensitivity analyses presented in the section "Additional exploratory analyses undertaken by the ERG".

Retreatment interval of RTX

The company used a 6-month treatment interval and referred to the Summary of Product Characteristics (SmPC) for RTX[4] and the NICE TA195[3] guidance to justify the 6-month retreatment interval. The ERG notes that the SmPC states that "need for further courses should be evaluated 24 weeks following the previous course. Retreatment should be given at that time if residual disease activity remains". In addition, the guidance for TA195 states that the Committee considered that treatment "was unlikely to be as frequent as every 6 months for every person receiving rituximab." Therefore, the ERG does not consider that either source justifies using a 6-month retreatment interval.

However, after further consideration of the evidence, the ERG decided to use a different retreatment interval of RTX from that used in the original ERG report. Published data from the SUNRISE trial[5] indicate that two courses of rituximab given over 48 weeks result in a statistically significantly higher ACR 20 response rate at 1-year compared with a single course given over the same period. Taking into account that the efficacy of RTX + MTX used in the model was based on data from the REFLEX trial,[6] the ERG consider that the retreatment interval used in the model should be the mean retreatment interval from REFLEX (307 days), instead of the estimate used in the original ERG report (7.35 months). Using a different retreatment interval would introduce an inconsistency with the efficacy estimates. The ERG notes that a retreatment interval of 307 days (10.09 months) is closer to the 9-month retreatment interval assumed by the AG in TA375,[7] that was uncontested at the time by the company.

Summary of the company's new analyses

In their response to the ACD, the company present the results of the analyses based on the ERG's amended model after applying the three changes discussed above. The company considered a sequence where CZP in combination with MTX was provided after RTX + MTX not to be relevant to the final scope of this appraisal. However, it included a sequence where CZP + MTX replaces RTX + MTX.

The results of the company's base case analysis are shown in Table 2. The sequence including CZP + MTX before RTX + MTX was estimated to produce 0.42 extra QALYs at an additional cost of £10,763 compared with the currently recommended sequence (RTX + MTX sequence), resulting in an

ICER of £25,682 per QALY gained. The sequence including CZP + MTX instead of RTX + MTX was extendedly dominated by the RTX + MTX sequence and the CZP + MTX before RTX + MTX sequence.

Table 2: Results of the company's base case analyses

Sequences	Total QALY	Total cost (£)	Incremental QALY	Incremental cost (£)	ICER (£/QALY)
RTX + MTX	7.266	119,814	-	-	
CZP+MTX instead of RTX+MTX	7.293	123,281	0.03	3,467	130,382*
CZP+MTX before RTX+MTX	7.685	130,577	0.42	10,763	25,682

*Extendedly dominated

The company undertook a series of scenario analyses to assess the impact of the different assumptions for treatment duration and retreatment interval of RTX. The cost-effectiveness estimates for CZP + MTX before RTX + MTX compared with RTX + MTX ranged from £17,293 per QALY when using treatment duration estimates based on Ramiro *et al.*[1] and a 6-month retreatment interval for RTX to being dominated when using treatment duration estimates based on Du Pan *et al.*[2] The CZP + MTX instead of RTX + MTX was either dominated or extendedly dominated by the other two sequences except: in the scenario where treatment duration was based on Ramiro *et al.*,[1] where the ICER for the CZP + MTX instead of RTX + MTX sequence compared with the RTX + MTX sequence was £16,230 per QALY gained; and in the scenario where treatment discontinuation was based on Du Pan *et al.*,[2] where the ICER of the RTX + MTX sequence compared with the CZP + MTX instead of RTX + MTX was estimated to be £4,698 per QALY gained.

Additional exploratory analyses undertaken by the ERG

The ERG undertook additional exploratory analyses based on the company's new base case analysis, to which the ERG applied two changes: using the treatment duration estimates used in TA195 and in the ERG report, and; using the RTX retreatment interval of 307 days as reported in the REFLEX trial. Therefore, the differences between this base case and the ERG's base case in the original ERG report would be: setting RTX retreatment interval to 307 days instead of 7.35 months; and fixing the error introduced in the ERG's amended model and identified by the company.

The results of the ERG's base case analysis are summarised in

Table 3: the RTX + MTX was estimated to be both more effective and less costly and therefore dominated the other two sequences.

Table 3: Results of the ERG's base case analysis

Sequences	Total QALY	Total cost (£)	Incremental QALY	Incremental cost (£)	ICER (£/QALY)
CZP+MTX instead of RTX+MTX	7.444	129,746	-	-	Dominated
CZP+MTX before RTX+MTX	8.047	131,106	-	-	Dominated
RTX + MTX	8.148	117,272	-	-	

The ERG performed additional scenario analyses to assess the impact of the treatment duration assumption and the retreatment interval of RTX in the cost-effectiveness estimates. Assuming equal treatment duration for all bDMARDs, the ICER of CZP+MTX before RTX+MTX compared with RTX + MTX is estimated to be £36,113 per QALY gained (see **Error! Reference source not found.**). If equal treatment duration for all bDMARDs and the retreatment interval of RTX used by the AG in TA375[7] (9 months) is used in the model, the ICER of CZP+MTX before RTX+MTX compared with RTX + MTX decreases to £34,265 per QALY gained (see **Error! Reference source not found.**).

Table 4: Results of the scenario analysis assuming equal treatment duration for all bDMARDs

Sequences	Total QALY	Total cost (£)	Incremental QALY	Incremental cost (£)	ICER (£/QALY)
RTX + MTX	7.266	110,373	-	-	
CZP+MTX instead of RTX+MTX	7.293	123,281	0.027	12,908	485,388*
CZP+MTX before RTX+MTX	7.685	125,508	0.419	15,136	36,113

*Extendedly dominated

Table 5: Results of the scenario analysis assuming equal treatment duration and a retreatment interval of RTX of 9 months (as in TA375)[7]

Sequences	Total QALY	Total cost (£)	Incremental QALY	Incremental cost (£)	ICER (£/QALY)
RTX + MTX	7.266	112,046	-	-	
CZP+MTX instead of RTX+MTX	7.293	123,281	0.027	11,235	422,474*
CZP+MTX before RTX+MTX	7.685	126,407	0.419	14,361	34,265

*Extendedly dominated

Conclusions

The company presented new analyses for population A (patients for whom RTX + MTX is still a treatment option) based on the ERG's amended model, to which they applied three changes: assuming equal treatment duration for all bDMARDs; assuming a 6-month retreatment interval for RTX; and fixing an error introduced in the amended model by the ERG. The company referred to evidence to support these two alternative assumptions and presented the results for the new analyses, which resulted in an estimated ICER of £25,682 per QALY gained for the sequence including CZP + MTX before RTX + MTX compared with the currently recommended sequence (RTX + MTX). The company also presented results for scenario analyses assessing the impact of these assumptions in the cost-effectiveness estimates.

The ERG critiqued the assumption of equal treatment duration for all bDMARDs and the 6-month retreatment interval of RTX. The ERG argued that the treatment duration estimates used in TA195 are the best estimates for the treatment duration of RTX and that the retreatment interval should be based on the REFLEX trial because the efficacy of RTX + MTX was estimated from data collected in this trial. The ERG's base case analysis, which differed from the company's analysis in terms of the estimated treatment duration for RTX (based on TA195) and retreatment interval of RTX (307 days), resulted in the currently recommended sequence (RTX + MTX) dominating the sequences where CZP + MTX was provided before or instead of RTX + MTX. The ERG undertook a series of scenario analyses to assess the impact of the assumptions on treatment duration and retreatment interval of RTX on the results. Across the range of cost-effectiveness estimates for the sequence featuring CZP + MTX before RTX + MTX compared with the RTX + MTX sequence, the lowest ICER was £34,265 per QALY gained when assuming equal treatment duration for all bDMARDs and a retreatment interval of 9 months for RTX.

Finally, as stated in the ERG report, the ERG believes that the methodology for modelling first and subsequent treatments is limited and can result in implausible results when comparing elongated sequences, or when the duration of the first treatments in the sequences compared are significantly different to each other. As such, the ERG believes that the credibility of comparisons of sequences of different lengths within the model is limited.

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