NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed

10th July 2015

UCB Response to the Appraisal Consultation Document

Summary of UCB Response to the ACD

UCB welcome the opportunity to comment on the Appraisal Consultation Document (ACD).

We welcome the preliminary decision to recommend adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept as treatment options for patients living with severe rheumatoid arthritis (RA)

Following the review of the ACD, UCB would like to make the following key points, some of which have been raised previously during the consultation of the initial Assessment Group (AG) report:

- **Exclusion of UCB key registration trials:** The Committee recognises the importance of considering the Assessment Group's network meta-analysis that considered the wider and complete range of trials; however, the main results reported in Table 3 of the ACD (EULAR response, Populations 2 and 3) are not from this complete network, but from the analysis where the key registration trials of certolizumab pegol (CZP), among others, have been excluded. UCB re-emphasise that the RAPID studies are appropriate and within scope for inclusion and request that they are considered part of the main analysis and that the EULAR response results from this wider complete network is presented within the base case analysis in the final guidance document.
- **Moderate RA population:** Following this preliminary guidance, access to biologics in the UK is still restricted to a much greater extent than seen in the rest of Europe. Moderate RA has a significant burden for patients and for society as a whole. There is a sub-set of moderate patients for which biologic therapy is cost-effective; UCB would like to understand further why the Committee has come to a different decision for these moderate patients than for severe patients.

Elaboration on these key points and other comments are presented under the questions asked by NICE, in terms of consideration of the relevant evidence, its interpretation and whether the provisional recommendations are sound.

Detailed UCB Response to the ACD

1 Has all the relevant evidence been taken into account?

1.1 Exclusion of UCB key registration trials

UCB welcomes the acknowledgement that the Committee gives in the ACD to the AG's sensitivity analysis where a wider and complete network of trials was employed, including those trials with a small proportion of patients who had prior biologics, which reflects the discussions that took place during the last Committee meeting.

UCB is pleased that the ACR responses from this analysis of the complete network are presented in Table 4, but are Table 4, but are concerned that the EULAR responses presented in Table 3 (p.21) in the ACD remain those from the AG's those from the AG's primary analysis where the main registration Phase III trials for certolizumab pegol (CZP) (the (CZP) (the RAPID studies) were excluded. Currently, the only CZP trial that the Assessment Group includes in their

includes in their primary analysis of the moderate to severe population (Populations 2 and 3 combined) is the CERTAIN study, conducted in low to moderate RA patients only (see Appendix for Section 1.1

Table 2 in Appendix for an overview of the CZP studies included and excluded in the AG network meta-analysis).

The inclusion of patients with prior experience of biologics would have minimal impact on the results. Post-hoc analyses were conducted on the RAPID 1 and 2 studies, by excluding those subjects with prior biologic exposure (3.5% (34/982) and 4.8% (30/619) from the ITT, respectively). The exclusion of the small subset of patients [redacted] with prior biologic exposure had no impact on the main results or primary conclusions of the studies in terms of ACR20 at Week 24 (Figure 1). Similarly, the conclusions were maintained for ACR50/70 and EULAR responses (Appendix Table 3 and Table 4).

The consideration of the CERTAIN trial (conducted in low to moderate RA patients) as the only relevant evidence of the efficacy for CZP in the primary AG analysis in the combined moderate and severe RA populations, penalizes CZP and biases the results to be more in favour of the other biologics over CZP. UCB is concerned that the current main AG analysis therefore provides a misleading conclusion to health care professionals, as it does not accurately reflect the evidence base for CZP in severe RA patients. The two registration RAPID studies for CZP, which have been excluded from the AG's primary analysis, represent a very large clinical program, with over 1,275 RA patients in the active arms,[1, 2] and have supported the current CZP license in Europe.[1] These trials have also been acknowledged and accepted in the previous NICE positive recommendation of CZP (NICE TA186, 2010).[2]

UCB re-emphasise that the RAPID studies are appropriate and within scope for inclusion and request that they are considered part of the main analysis and that the EULAR response results from this wider complete network is presented within the base case analysis in the final guidance document. It is important that all the clinical evidence presented in the final guidance document includes the CZP pivotal registration studies to accurately reflect its proven efficacy within its EU license and in the population under evaluation in this MTA.

Figure 1. Comparison of ACR20 response at week 24 from RAPID1 and RAPID2 in the ITT trial populations (Keystone 2008[3]; Smolen 2009[4]) and the prior biologic naïve subpopulation (post-hoc analysis, data on file)

[redacted]

1.2 RAPID2 EULAR response data

The RAPID2 study was not included in the AG's wider network for EULAR response as this data is not published and was not provided in our original submission. Please find below in Table 1 the EULAR response data for the intention-to-treat population of RAPID2. If possible, we would ask that the AG's sensitivity analysis on the wider network for EULAR response be updated to include this additional data.

Table 1. RAPID2 EULAR response data

	CZP 200 mg +MTX N=246	PBO +MTX N=127
Week 12		
Moderate EULAR response[b], %	[redacted]	[redacted]
Good EULAR response[b], %	[redacted]	[redacted]
Good EULAR response, OR (95% CI) vs PBO	[redacted]	[redacted]
Week 24		
Moderate EULAR response[b], %	[redacted]	[redacted]
Good EULAR response[b], %	[redacted]	[redacted]
Good EULAR response, OR (95% CI) vs PBO	[redacted]	[redacted]

ITT population. [b]LOCF. *P<0.001 CZP vs. PBO. **P<0.01 CZP vs. PBO

1.3 Exclusion of certolizumab pegol monotherapy data

UCB would like to raise the point that the evidence for CZP in monotherapy has been excluded from the Assessment Group's NMA despite the approved EU license and supportive evidence (the FAST4WARD and HIKARI studies).

FAST4WARD was originally not considered by the AG due to the 4-weekly dosing that was used in this trial (see Appendix for Section 1.1

Table 2 in the Appendix). UCB would like to note that the 4-weekly dosing was included within the CZP SmPC as of November 2013. The FAST4WARD data for ACR20/50/70 response, which was presented in the UCB original submission, is shown again in the Appendix of this document (Figure 2); the EULAR response data is not available for this trial. For the HIKARI study, we provided the ACR20 results at week 12 for the monotherapy subgroup within our original submission, and this is also presented again in the Appendix (Figure 3).

We would therefore ask that the FAST4WARD and HIKARI studies are considered as relevant evidence for CZP in monotherapy and that the following sections of the ACD are updated:

- Table 3, page 21, which currently does not include CZP monotherapy
- Section 4.1.10 on the assessment group's wider network of trials it is stated that: "This allowed the inclusion of all biological treatments, with the exception of certolizumab pegol monotherapy."

Given that the current decision to not recommend biologic monotherapy leaves the patient group who cannot take methotrexate with very few therapeutic options (see section 3.2 of the present response), the Committee should ensure that they are appraising all the available evidence for the final guidance.

2 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

2.1 ICER for monotherapy in moderate population

Section 4.2.35 of the ACD summarises the results for biological DMARD monotherapy for moderate active rheumatoid arthritis previously treated with methotrexate (MTX) and indicates that results for this population were provided by AbbVie and UCB. Section 4.2.18 also mentions that UCB provided analysis of CZP monotherapy in the moderate population.

We would like to clarify that UCB did not conduct any cost-effectiveness analysis of biologic monotherapies in moderate RA patients previously treated with MTX. The following inaccuracies have therefore been identified:

- Section 4.2.18 incorrectly suggest that UCB submitted a moderate monotherapy model. We ask that this section is re-phrased to: "UCB submitted analyses for the severe active (as monotherapy and with methotrexate) and moderate active populations (with methotrexate only) who had previously had methotrexate."
- Section 4.2.35: the ICER of £49,226 reported in this section was for CZP + MTX versus conventional DMARDs in the moderate population, not for CZP monotherapy as the text implies. This reference to the UCB submission should be removed completely from this section.
- Section 4.2.27 reports an ICER of £47,821 for CZP in combination with MTX compared to conventional DMARDs. We would like to clarify that the ICER of £47,821 was for CZP + cDMARDs, and not CZP + MTX (which is £49,226 as reported above). The ICER reported in Section 4.2.27 should therefore be changed to £49,226 per QALY.

UCB requests that sections 4.2.17, 4.2.18 and 4.2.35 are revised to accurately reflect the results submitted by UCB.

3 Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

3.1 Moderate RA population

Following the draft guidance in the ACD, access to biologics in the UK is still restricted to a much greater extent than seen in the rest of Europe, meaning that the UK will lag behind its European counterparts in terms of the quality of care that patients with RA receive. The latest BSR biologics guidelines recommend that biologics can be initiated for moderate patients with a DAS-28 >3.2, and they justify this extensively by citing evidence from the ERAN and ERAS databases that show that the majority of RA patients with a DAS-28 of 3.2-5.1 at 3 years have only marginally better functional, radiological and orthopaedic outcomes at 5 years when compared with those with a DAS-28 > 5.1, indicating that the burden of moderate RA is similar to that of severe RA.[5] As indicated in the UCB original submission, it is recognised that there is a substantial burden (including pain, fatigue and loss of physical function) associated with patients exhibiting moderate disease activity. Furthermore, it is well established that in patients with moderate disease activity, radiographic progression (evidence of joint damage visible and measurable via X-ray) can continue, which can lead to permanent loss of function and disability. This can have a significant impact on patients' ability to work and therefore moderate RA imposes a substantial productivity cost to society.

The importance of treating patients with moderate disease activity is well acknowledged, and the efficacy of anti-TNFs in patients with moderate disease activity has been demonstrated in both clinical trials and registries. For example, Hyrich et al. (2009) demonstrated that treatment of patients with moderate disease activity with anti-TNF therapy confers substantial benefits based on an analysis of the British Society for Rheumatology Biologics Registry (BSRBR). Additionally, the open-label run-in PRESERVE trial of etanercept and the randomised controlled CERTAIN trial of CZP show clear benefits of anti-TNF use in a moderate disease activity population.

Although treatment with biologics may not be cost-effective in the overall moderate disease population, the AG analysis has shown that there is a sub-set of the moderate patients who have the greatest HAQ progression for which biologic therapy is cost-effective (ICER = £28,500 per QALY). The single statement in Section 4.3.22 that "*the Committee was not persuaded that the exploratory analysis for the moderate active group was as applicable to this group as to the severe active group*", does not give any explanation or justification for why the Committee came to this conclusion. UCB would like to understand further why the Committee has come to a different decision for moderate patients than for severe patients who have the greatest HAQ progression.

3.2 Recommendations on monotherapy

UCB are concerned that the Committee came to the conclusion that they were "*not persuaded that biological DMARDs were a cost-effective use of NHS resources when used as monotherapy*" (Section 4.3.23), whereas previously NICE recommended specific biologics, including certolizumab pegol as monotherapies, when continuing methotrexate is not appropriate (TA186[2], TA130[6]).

UCB would like to highlight that this leaves a significant number of patients who are intolerant or contraindicated to methotrexate without access to biologic therapy. These patients have few other options and therefore would continue to suffer with high disease activity, poor functioning and low quality of life. Disease severity and disability are also linked to premature mortality in patients with RA.[7]

Similarly to the overall severe RA population, there will be those patients who cannot take methotrexate who are at high risk of HAQ progression and for whom biologic therapy is cost-effective. UCB hopes that the Committee will reconsider their decision over monotherapy, particularly in light of the additional evidence that should now be taken into consideration in the analysis (see Section 1.3) and in such a case where there is no alternative therapy that the Committee are willing to accept a higher degree of uncertainty around the ICERs.

4 Position on biosimilars

UCB acknowledge NICE's position on appraising biosimilars through multiple technology appraisals. We recognise that the inclusion of the infliximab biosimilars was not in the original scope but understand the reasons for their inclusion at this later stage. We would like to highlight that biosimilars should not be considered interchangeable with their originator brands, as supported by the MHRA biosimilar guidelines,[8] and hope that any NICE guidance reflects this.

5 Comments on the AG's executable model

Issue 1 Error in calculating MTX Response and LEF Response monitoring costs

Description of problem	Description of proposed correction	Result of amended model or expected impact on the result (if applicable)
Worksheet "**Costs**": there is an error in the formula in **Cell D89** which does not account for the right unit costs (c_mtx_response_mon): =SUMPRODUCT(D82:I82,D88:I88) = £1,700	Revise formula to: "=SUMPRODUCT(**D77:I77**,D88:I88) **=** £1340"	Expected minimal impact on the ICER, although not all AG analyses and scenarios were tested
Worksheet "**Costs**": there is an error in the formula in **Cell D91** which does not account for the right unit costs (c_lef_response_mon): =SUMPRODUCT(D84:I84,D90:I90) = £1,645	Revise formula to: =SUMPRODUCT(**D77:I77**,D90:I90) =£1590	Expected minimal impact on the ICER, although not all AG analyses and scenarios were tested

Issue 2 Error in calculating initial treatment cost for certolizumab pegol

Description of problem	Description of proposed correction	Result of amended model or expected impact on the result (if applicable)
Worksheet "**Costs**": in **cell G11** (c_r_CTZ), the formula to calculate the CTZ response cost is wrong. Firstly, not all loading doses have been accounted for, the cost of 3 loading doses should be applied. Secondly, an additional month's worth of monitoring and administration costs have been included in the response period.	The formula in cell G11 should be replaced with: =(c_CTZ*6)+c_bio_pre_tx_mon+c_bio_response_mon-(7*S11) = £4514.65	Expected minimal impact on the ICER, although not all AG analyses and scenarios were tested

Appendix

Appendix for Section 1.1

Table 2. Overview of certolizumab pegol (CZP) trials included in the original UCB submission and in the AG's analysis (AG report and amendments, 2015)

Trials	Included in the UCB original submission[9]	Included in AG's 'main analysis'?	Included in AG's sensitivity analysis (wider network)?
RAPID 1 (Keystone 2008[3])	**Yes** (Population 2; Combination therapy)	**No** (due to 4% with prior biologic experience)	**Yes** (Populations 2 and 3 combined)
RAPID 2 (Smolen 2009[4])	**Yes** (Population 2; Combination therapy)	**No** (due to 1.6% with prior biologic experience)	**Yes** (ACR response only) (Populations 2 and 3 combined)
REALISTIC (Weinblatt 2012[10])	**Yes** (Population 2; Combination therapy and monotherapy separately)	**No** (due to no biologic-naïve ACR/EULAR data at 22-30 weeks)	**No**
J-RAPID (Yamanaka 2012[11])	**Yes** (Population 2; Combination therapy)	**No** (due to 16% with prior biologic experience)	**Yes** (Populations 2 and 3 combined)
HIKARI (Yamanaka 2012[12])	**Yes** (Population 2; Combination therapy and monotherapy separately)	**No** (due to the claim by the AG that data for CZP+MTX and monotherapy were not available separately – this was, however presented in the original UCB submission)	**No**
RA0025 (Kang 2012[13])	**Yes** (Population 2; Combination therapy)	**No** (due to 15% with prior biologic experience)	**Yes** (ACR response only) (Populations 2 and 3 combined)
FAST4WARD (Fleischmann 2009[14])	**Yes** (Population 2; Monotherapy)	**No** (due to 4-weekly dosing*)	**No**
CERTAIN (Smolen 2011[15])	**Yes** (Population 3; Combination therapy)	**Yes** (Population 2 and 3 combined)	**Yes** (Population 2 and 3 combined)

Population 2: adults with severe (DAS28 score ≥5.1) active RA that have been previously treated with cDMARDs but not bDMARDs; Population 3: adults with moderate to severe active RA (DAS28 between 3.2 and 5.1) that have been previously treated with cDMARDs only, including methotrexate (unless contraindicated or inappropriate).

*4-weekly posology has been licensed for CZP since November 2013; please see Section 1.3 for further details

RAPID1 and 2 biologic naïve population

Table 3. RAPID 1 study: post-hoc analysis of the efficacy in biologic naïve population only (data on file),

	Primary analysis ITT population (Keystone 2008[3])		**Post-hoc analysis Biologic naïve population**	
	CZP 200 mg +MTX n=393	**PBO + MTX n=199**	**CZP 200 mg +MTX n=382**	**PBO + MTX n=192**
Week 12				
Good EULAR response, OR (95% CI) vs PBO	[redacted]		[redacted]	-
Week 24				
ACR20 response				
% responders	[redacted]	13.6%	[redacted]	[redacted]
OR (95% CI) vs PBO	[redacted]	-	[redacted]	-
ACR50 response				
% responders	37.1%†	7.6%	[redacted]	[redacted]
OR (95% CI) vs PBO	[redacted]	-	[redacted]	-
ACR70 response				
% responders	21.4%†	3.0%	[redacted]	[redacted]
OR (95% CI) vs PBO	[redacted]	-	[redacted]	-
Good EULAR response, OR (95% CI) vs PBO	[redacted]	-	[redacted]	-

Biologic naïve population. †P<0.001. *Post-hoc nominal p-value P<0.001 CZP vs. PBO. ACR response and EULAR response were assessed by logistic regression.

Table 4. RAPID2 study: post-hoc analysis of the efficacy in biologic naïve population (data on file)

	Primary analysis ITT population (Smolen 2009[2])		Post-hoc analysis Biologic naïve population	
	CZP 200 mg +MTX n=246	**PBO + MTX n=127**	**CZP 200 mg +MTX n=237**	**PBO + MTX n=121**
Week 12				
Good EULAR response, OR (95% CI) vs PBO	[redacted]	-	[redacted]	-
Week 24				
ACR20 response				
% responders	57.3%†	8.7%	[redacted]	[redacted]
OR (95% CI) vs PBO	[redacted]	-	[redacted]	
ACR50 response				
% responders	32.5%†	3.1%	[redacted]	[redacted]
OR (95% CI) vs PBO	[redacted]	-	[redacted]	
ACR70 response				
% responders	15.9%††	0.8%	[redacted]	[redacted]
OR (95% CI) vs PBO	[redacted]	-	[redacted]	-
Good EULAR response, OR (95% CI) vs PBO	[redacted]	-	[redacted]	-

Biologic naïve population. †P<0.001. ††P<0.01. *Post-hoc nominal p-value P<0.001 CZP vs. PBO. ** Post-hoc nominal p-value P<0.01 CZP vs. PBO. ACR response and EULAR response were assessed by logistic regression.

Appendix for Section 1.3

CZP monotherapy data

Figure 2. FAST4WARD study: ACR responder rates at week 24 (ITT population)[14]

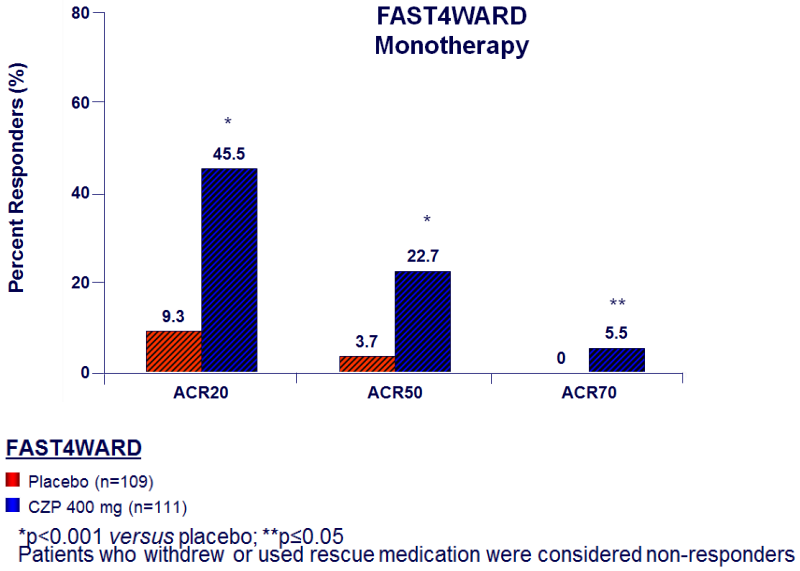
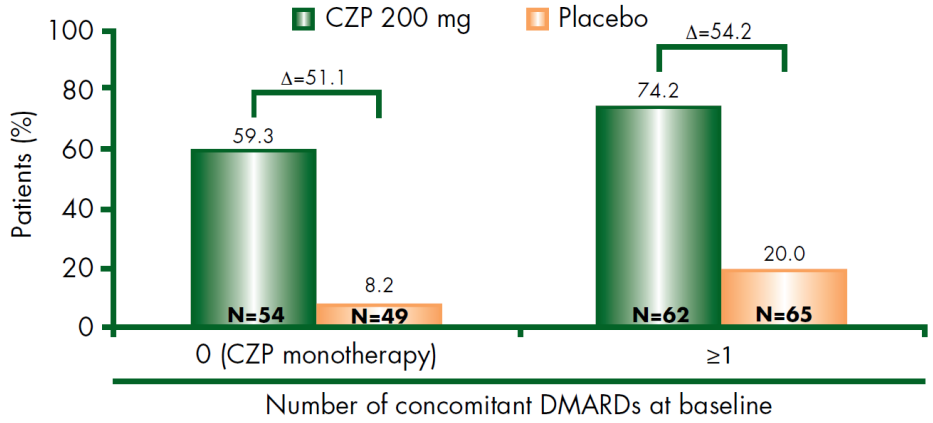


Figure 3. HIKARI study (Japanese RA patients): ACR20 response rates at week 12 by baseline concomitant DMARDs use (0 or ≥1) (NRI)[12, 16]



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