NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233)

February 2015

UCB Response to Assessment Group Report

UCB welcomes the opportunity to respond to the assessment group's report on the use of anti-TNFs in ankylosing spondylitis (AS) and axial spondyloarthritis (axSpA) without the radiographic evidence of AS (nr-axSpA). Following a review of the report we would like to provide a number of comments and observations for the NICE committee, which we believe have significance for the discussion at ACD1.

Outline of Responses

UCB has structured its comments into two discrete sections:

Section 1: General responses to report and modelling approach

Section 1 highlights some of the key issues UCB has concerns over with regards to the assessment group's report, particularly in relation to some of the disease background descriptions of axSpA and approaches taken by the assessment group in analysing these patients.

- Clarification of the axSpA classification criteria and the axSpA disease continuum
- Choice of studies included within the assessment group's mixed treatment comparison for the nr-axSpA subpopulation
- RAPID-axSpA was the only study reviewed by the assessment group that recruited patients that reflected the EU licence population
- Clarification of reporting of adverse events for anti-TNFs

Section 2: Clarification of the evidence of certolizumab pegol and UCB's original submission

Section 2 is split into two key subsections that are aimed at resolving (1) a number of inaccuracies in the assessment group's report with regards to the evidence of certolizumab pegol and the RAPID-axSpA study, and (2) how the assessment group have interpreted the modelling approach employed by UCB in the original submission. This subsection reiterates the justifications and approaches used in the original model.

UCB Response to Assessment Group Report

1 General responses to report

1.1 Clarification of the axSpA classification criteria

The assessment group states in their report (page 30) that "*there is some concern that the diagnostic criteria for nr-axSpA may be too liberal and may include patients who do not have axSpA and will never progress to AS, particularly with respect to patients who are diagnosed without evidence of imaging (MRI) changes*". Furthermore, the assessment group also states that "*early disease (nr-axSpA) may be less readily diagnosed and patients offered fewer treatment options even though it can be as, or even more, debilitating that established AS*" (page 30).

We would like to note that currently there is no diagnostic criteria for axSpA, as is the case for most other rheumatic diseases. What does exist is the classification criteria for axSpA developed by the Assessment of SpondyloArthritis International Society (ASAS), which should only be applied once a diagnosis has been made to define a homogeneous population. The classification criteria should not be used to make a diagnosis. Furthermore, the performance of the ASAS classification criteria for axSpA are sound,[1, 2] and perform better in terms of sensitivity and specificity to the 2010 ACR/EULAR classification criteria for rheumatoid arthritis.

Historically, patients with axSpA were only identified when there was evidence of structural damage in the sacroiliac joints on x-ray (according to the modified New York [mNY] criteria); ie. when they had AS. However, advances in the understanding of axSpA have highlighted that some patients have clinical manifestations before radiographic sacroiliitis is apparent (nr-axSpA). Therefore, both AS and nr-axSpA represent the spectrum of axSpA, with the presence or absence of radiographic sacroiliitis as the only differentiating clinical feature. Additionally, using radiographs to make a diagnosis of axSpA creates several challenges. Structural changes may take many years to develop (if at all), which result in a long delay in diagnosis (typically 5-10 years). Finally, there is a great deal of

variability in the interpretation of sacroiliac joint x-rays when assessing sacroiliitis. The availability of MRI has facilitated visualisation of inflammatory changes before structural changes occur on x-rays. Importantly, patients with nr-axSpA and AS have the same clinical features and level of disease activity (eg. BASDAI) and pain independently of whether they are classified as having nr- axSpA or AS.

Treatment of axSpA patients should be based on clinical signs and symptoms and not on whether patients may progress from nr-axSpA to AS, which the assessment group would seem to suggest Evidence from real-life cohorts have shown that the burden of nr-axSpA is similar to AS,[3, 4] and therefore these patients should be entitled to the same effective treatment options.

In the UK, rheumatologists use clinical judgement to diagnose axSpA, which may be supplemented using the classification criteria: "*In order to diagnose our patients appropriately, clinical judgement is critical to avoid misdiagnosis, classification criteria can aid diagnosis but are not commonly used to determine a diagnosis. Typically a rheumatologist when considering a diagnosis of nr-axSpA in a patient with inflammatory back pain would perform an MRI scan looking for evidence of active sacroiliitis or active inflammation at other spinal sites check a CRP, HLA B27 status and take a history including evidence of previous enthesitis, psoriasis or inflammatory bowel disease.*"[5]

Furthermore, axSpA is typically viewed by clinicians in the UK as a disease continuum; the only differentiating clinical feature of the AS and nr-axSpA subpopulations is the presence or absence of radiographic evidence of AS. Again, progression to AS is neither a defining, nor clinically relevant feature of axSpA and likewise, the main aim of axSpA treatments such as anti-TNFs are to maximise long-term health-related quality of life and social participation through control of signs and symptoms, prevention of structural damage, normalisation or preservation of function, avoidance of toxicities and minimisation of comorbidities.[6]

UCB would request that the assessment group revise their statement in line with the clarifications expressed above.

1.2 Inclusion of infliximab in the assessment group's mixed treatment comparison for the nr-axSpA subpopulation

The assessment group states on page 23 of their report that their objective was to "*determine the clinical effectiveness, safety, and cost-effectiveness within the NHS of adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab, within their respective licensed indications, for the treatment of severe active AS, or severe nr-axSpA*". However, on page 40 of the assessment group report it is stated that "*The Barkham 2009 trial of infliximab in nr-axSpA patients (see Table 2) was included in the clinical efficacy section because, even though infliximab is not currently licensed for patients with nr-axSpA, the dose used in this trial was the same as that licensed for AS*".

Infliximab is an anti-TNF that is currently licenced in the EU for the treatment of patients with ankylosing spondylitis, but not licensed for the treatment of nr-axSpA. To date, one study assessing the efficacy of infliximab in the nr-axSpA population has been conducted (Barkham 2009), in a small number of patients. The study inclusion was based on the Calin criteria, and enrolled mixed subpopulations of axSpA patients, with 12% of patients fulfilling the mNY criteria for AS.

Given that infliximab does not have a licence in the EU for the treatment of nr-axSpA, UCB would request further clarification of why the Barkham 2009 study was included in the assessment group's evaluation of clinical effectiveness of anti-TNFs for patients with nr-axSpA, and how the evidence from this study was considered in the evaluation. Furthermore, UCB would request that a sensitivity analysis is performed that excludes data from Barkham 2009.

1.3 Baseline CRP in patients with nr-axSpA

In their analysis of clinical effectiveness, the assessment group states on page 68 that *"heterogeneity of CRP levels was evident across both the AS trials and the nr-axSpA trials"* and discusses this heterogeneity, particularly with regards to the comparatively lower CRP levels in nr-axSpA subpopulation. The assessment group report also states that *"In the nr-axSpA trials only the RAPID-axSpA population came close to this [14 mg/l] cut-off"*.

UCB would like to note that out of the included trials, RAPID-axSpA is the first randomised, placebo-controlled, multicentre registration study to examine the efficacy of an anti-TNF therapy across the spectrum of axSpA patients rather than in individual AS and nr-axSpA subpopulations. The study allowed for a direct comparison of the burden of disease and efficacy of certolizumab pegol treatment in AS and nr-axSpA patients, as classified by the ASAS criteria. Furthermore, RAPID-axSpA recruited nr-axSpA participants that reflect the current licence, whilst the inclusion criteria of the other studies did not meet the licence criteria, as reflected by the lower baseline levels of CRP in those studies.

UCB would request that the assessment group report accurately reflects the fact that the RAPID-axSpA study recruited participants as per the licence, and therefore accurately reflects the treatment population as per the scope of this technology appraisal.

1.4 Assessment Group's reporting of the adverse events for anti-TNFs

1.4.1 Limitations of reporting serious infection rates

The availability of safety data for anti-TNFs is fairly limited, especially within the axSpA indication. It is common for analyses of adverse events from trials of anti-TNFs to include safety data across different indications. This is the case for the different reviews and meta-analyses evaluated in the assessment group report, which were not based on axSpA-specific populations. Although studies are combined in a meta-analysis to increase power, a number of caveats exist in doing so.

For example, the authors of the Cochrane meta-analysis, which is reviewed by the assessment group, acknowledge several limitations of their meta-analysis that are not reported in the assessment group's report.[7] Specific limitations that affect the interpretation of their results, since they relate to the serious infection rate for certolizumab pegol include, (1) inadequate adjustment for treatment exposure, (2) methodological challenges associated with dealing with zero incidence of serious infections in the placebo groups, and (3) the substantial heterogeneity associated with pooling data from all placebo controlled studies across all agents and all disease indications.

UCB request that the limitations of the different reviews of safety data identified by the assessment group are acknowledged in the report (for example, page 90).

1.4.2 Summarisation of adverse events

On pages 26, 88 and 93 of the assessment group's report, the authors summarise *"certolizumab pegol is associated with significantly higher rates of serious infections and serious adverse events*" when compared with control treatments. These conclusions are made with little context provided, are stated as matter-of-fact, and do not reflect that these are the conclusions of the Cochrane review.

UCB would request that additional context is added when the results of independent meta-analyses such as the Cochrane review are summarised, and refer to the limitations inherent in such analyses (see response 1.4.1 above).

1.5 The nature of ICERs

The assessment group commented on page 159 of their report that the "*ICERs from manufacturers are speculative and highly uncertain"*).

While UCB acknowledge that generally ICERs are the result of modelling assumptions and subject to a level of uncertainty, and thus need to be tested through sensitivity analyses, UCB disagrees with the above comment on the speculative nature and high uncertainty of the ICERs.

The uncertainty within the submitted models was explored through extensive sensitivity analysis, so although some uncertainty always exists within a model, this has at least been explored and quantified. Furthermore, the submitted models obtained remarkably similar ICERs for the AS subpopulation under differing assumptions in terms of rebound, BASDAI/BASFI progression and other structural modelling uncertainties. The observation that the York model provided similar ICERs also in the AS subpopulation serves as additional evidence for the robustness of ICERs under the numerous uncertainties.

UCB would request clarity around why the group considers that ICERs estimated by manufacturers are speculative and how the assessment group has explored the uncertainty within their model. Furthermore UCB also ask the group to revise their wording to reflect the consistency of the ICERs while reducing the emphasis that they are speculative and highly uncertain in the AS subpopulation.

2 Clarification of the evidence of certolizumab pegol and UCB's original submission

2.1 Certolizumab pegol and the RAPID-axSpA study

2.1.1 RAPID-axSpA study design

The assessment group summarizes the general characteristics of the trials included in its review in Table 2 (page 43) of their report. In Table 2, the trial length of RAPID-axSpA is presented as 96 weeks, and the placebo-controlled phase is presented as 12 weeks.

UCB would like to clarify that the RAPID-axSpA study is a Phase 3, 24 week placebo-controlled study with an open-label extension to 204 weeks,[8] as indicated in the manufacturer's submission.

UCB would request that the details in Table 2 be corrected in line with UCB's original submission to accurately reflect the design of the RAPID-axSpA study.

2.1.2 RAPID-axSpA baseline characteristics

The assessment group summarizes the baseline characteristics of the trials included in its review in Table 3 (pages 46 and 47) of their report.

UCB would like to clarify that the original submission included the baseline characteristics for SF-36 PCS, SF-36 MCS and ASQoL for both the AS and nr-axSpA subpopulations (UCB submission, page 26, table 5-5); however, these values were omitted from the assessment group's report in Table 3 (pages 46 and 47) when presenting the baseline characteristics of the RAPID-axSpA study.

UCB would request that the baseline values for these health-related quality of life outcomes be included in the assessment group's report.

2.1.3 Inclusion of ASAS50/70 data for certolizumab pegol

The assessment group's report states on page 58, that in the nr-axSpA subpopulation, *"Only one trial (RAPID-axSpA) reported ASAS 50 or ASAS 70 results*". In Table 112 of the assessment group report (binary response outcomes; page 256), ASAS50 and ASAS70 data for certolizumab pegol are not available, although ASAS50 and ASAS70 data for the nr-axSpA subpopulation are presented for ABILITY-1.

UCB would like to clarify that ASAS50 and ASAS70 data from the RAPID-axSpA study were not included as part of UCB's original submission. UCB would like the assessment group to clarify the source of these data presented on page 58 of their report.

2.1.4 Control of uveitis with anti-TNFs in patients with axSpA

Uveitis is common in patients with axSpA, with registry cohorts suggesting that approximately 17% of patients with axSpA also have a history of uveitis.[3, 9] In their report, the assessment group describe the data supporting the effect of anti-TNFs on the control of symptoms of uveitis. The assessment group report states on page 65 that *"Incidence of uveitis was also reported in one trial; up to the 24 week time point there were three cases in the etanercept arm and 8 cases in the placebo arm"*.

We would like to note that data from the RAPID-axSpA study indicated that the incidence rate of uveitis flares in patients with and without a history of uveitis was compared between placebo and active treatment. These data were included in UCB's original submission (page 34, table 5-11). During the 24-week double blind phase of the RAPID-axSpA study the incidence rate of uveitis in patients with a history of uveitis at baseline was lower in those treated with certolizumab pegol

compared to those treated with placebo. The incidence rate of uveitis in patients treated with certolizumab pegol were presented up to Week 48 (UCB submission, page 34, table 5-12).

UCB would request that the report is updated to include the uveitis data presented in the manufacturer original submission.

2.1.5 ASQoL data

The assessment group's report states on page 65 of their report that *"For ASQoL – a quality of life instrument specific to ankylosing spondylitis - ATLAS was the only trial which reported results together with SDs or SEs"*.

UCB would like to note that the ASQoL data was provided (in commercial in confidence) at Weeks 24, 48 and 96 in the AS and nr-axSpA subpopulations, in mean (SD) format (UCB submission, page 40, table 5-14).

UCB would request that these ASQoL data are considered in the assessment group's report. If the data are required in a different format then these can be made available to the assessment group.

2.1.6 Redacted data in tables

On pages 73–75 of the assessment group's report, the Week 96 data for certolizumab pegol is redacted. These data were not marked as commercial in confidence in the original submission (UCB submission, page 40) and should be visible in the assessment group report.

UCB would request that the redacting be removed from these outcomes.

2.1.7 Missing 2 year data for BASDAI, BASFI and BASMI

On page 75, the assessment group's report states that *"For certolizumab results for these outcomes [BASDAI, BASMI and BASFI scores] are only available up to one year (48 weeks)"*. On page 76, the assessment group report states that *"For certolizumab LOCF analysis at 48 weeks (n=97) gave a BASDAI final value of around 3, and a BASFI of around 2.5*".

UCB would like to note that in both cases, data up to Week 96 from RAPID-axSpA study were presented in the original submission (UCB submission, page 40).

UCB would like request that the text be revised to state that data are available up to two years, and that the Week 96 data from RAPID-axSpA submitted by UCB is accurately reflected in the assessment group report where necessary.

2.2 Clarification of the UCB modelling approach

2.2.1 Choice of Week 24 as anti-TNF response timepoint in AS

On page 132 of their report, the assessment group state that "*Response was assessed at 24 weeks in the AS subpopulation which was argued by the manufacturer to be in accordance with clinical practice as indicated key British opinion leaders. For the nr-axSpA subpopulation, response assessment was assumed at 12 weeks since comparator data were only available at that time point. In their base-case, the manufacturer used ASAS20 to determine response in line with the primary outcome measure in the RAPID-axSpA. However, it should be noted that ASAS 20 response at week 12 was the primary outcome in the RAPID-axSpA trial. Hence, while the measure of response used is in accordance with the primary outcome of the RAPID-axSpA trial, the differential timing of this applied across the separate populations clearly deviates from this. This has potential issues since at week 16, patients were allowed an 'early escape' from placebo and hence results at week 24 used for the AS subpopulation are no longer based on the original randomised population.*"

UCB would like to note that, as indicated in the original submission, the choice of the 24 week timepoint for the analysis is based on several factors. Firstly, a number of the studies included in the analysis presented data at the earlier timepoint around 12–16 weeks, but not all at Week 12, whilst a greater consensus was reported around the 24 week timepoint (UCB submission, section 6.6.1). Therefore, selection of the 24 week timepoint was made to also reduce the heterogeneity of the response within the analysis. Secondly, the choice of a 24 week assessment timepoint is motivated

by both actual clinical practise in the UK, supported by treatment guidelines, and the expert clinical opinion that if response has not been achieved by 12 weeks treatment with anti-TNF should be continued with reassessments up to 24 weeks. In particular, the ASAS explicitly note a change in their revised guidance for the timing assessment to be "Assessment after at least 12 weeks" whereas previously guidance was "Assessment between 6 and 12 weeks".[10] This practise is consistent with findings by the West Midland Rheumatology Audit,[11] cited by the NICE assessment group, that "*(i) the proportion of patients being assessed at 12 weeks after treatment initiation was sub-optimal; (ii) less than 20% of patients with an inadequate response at 12 weeks had their treatment discontinued*", implying that non-responders at 12 weeks are continuing anti-TNF treatment. For these reasons, we feel that the choice of 24 week assessment time in AS patients that is grounded in practise and expert guidance, is entirely natural, despite that the 12 week assessment was the primary endpoint for RAPID-axSpA.

With regard to the choice of a 12 week assessment for the nr-axSpA subpopulation, we emphasise that the more natural 24 week choice was not available, since comparator studies did not report assessment at this time point as their placebo controlled period was up to 12 weeks, whereas RAPID-axSpA was placebo controlled to 24 weeks.[12, 13]

UCB would thus like to request the assessment group to recognise in their report the rationale in using the 24 week timepoint in the submitted analysis by UCB. In addition UCB would request that the assessment group recognise that a sensitivity analysis in the AS subpopulation was performed, using the 12 week timepoint (UCB submission, sections 8.4.2.2 and 11.5.2.1.5).

2.2.1.1 Randomisation of placebo escape patients

On page 132 of their report, the assessment group states that "*This has potential issues since at week 16, patients were allowed an 'early escape' from placebo and hence results at week 24 used for the AS subpopulation are no longer based on the original randomised population*".

UCB would like to clarify that primary analysis of the efficacy outcomes at timepoints after the escape visit are based on the original randomization. As indicated in the UCB submission (page 21) all post Week 16 data for non-responding placebo patients who escaped were assigned to their original randomisation for Week 24 analyses. A non-responder imputation method was applied for binary outcomes (eg. ASAS20) and a last observation carried forward (LOCF) approach for continuous measures for the analyses at Week 24 (eg. BASDAI, BASFI), while maintaining their original randomisation.[8].

UCB would like to ask the assessment group to remove their wording of their statement that the "*subpopulation are no longer based on the original randomised population*", since it is incorrect.

2.2.2 Assessment group interpretation of the UCB model

2.2.2.1 Provision of BASDAI change scores conditional on response

In their report, the assessment group make the following statements:

- "*In addition, we requested additional data from the manufacturer on change scores conditional on response for certolizumab and placebo from the RAPID-axSpA trial but this was not provided. Hence, it is not possible to adequately assess the appropriateness of the method of adjustment used by the manufacturer to estimate change scores or the assumption applied to conventional care. However, it might be reasonable to assume that the actual conditional scores from RAPID-axSpA are unlikely to be higher than those reported here for certolizumab, since the manufacturer would presumably have responded to the request for the additional data if this had been the case.*" (page 135)
- "*Given that treatment continuation is determined by response to BASDAI50 at 12 weeks, it is important for the economic model to estimate the absolute change in BASDAI and BASFI separately for responders and non-responders, i.e. the conditional scores. However, the published clinical effectiveness evidence does not report the conditional scores. Consequently, we requested the conditional data from the pivotal trials in both the AS and nr-axSpA indications from each manufacturer. These data were subsequently provided by AbbVie, Pfizer, and MSD for their pivotal trials but not UCB*" (page 162)

- "*We requested the conditional data from the pivotal trials in AS from each manufacturer. These data were subsequently provided by several but not all manufacturers (AbbVie, Pfizer, and MSD).*" (page 176)

These data were provided by UCB to NICE on 13th October 2014. UCB therefore asks that the above statements claiming that UCB did not provide these data be removed, to accurately reflect the data provided by UCB in response to the request from NICE in October 2014. Moreover we ask that the assessment group report be revised to include and consider the data provided where appropriate. This applies to several places in the report including pages 135, 162, 176, Table 78, Table 80 and Table 138.

2.2.2.2 BASFI assumptions for patients receiving anti-TNFs

On page 137 of their report, the assessment group state: *"The assumption of no progression in BASFI for patients receiving anti-TNFs is not explicitly discussed within the manufacturer's submission, nor are separate results provided for alternative assumptions"*.

This assumption is explicitly discussed and justified in the UCB submission on page 68, where it is stated: *"It is assumed that patients who continue to respond and remain on anti-TNF therapy will thereafter maintain this improved BASDAI and BASFI score at a constant, unchanging level. This assumption has been generally accepted for biologic treatment in RA, based upon the evidence that functional deterioration might be prevented in those patients in whom the inflammatory process is controlled, as indicated by a sustained reduction in disease activity (although such evidence of disease modification in axSpA is lacking).[14, 15]"*

Moreover, the rate of change of BASFI for non-responders (applying to conventional care and those failing anti-TNF treatment) was systematically varied in all one-way sensitivity analyses and presented in Section 11.5.2 of the UCB submission (please see "Annual change in BASFI scores" bar in tornado diagrams). As the tornado diagrams show, UCB did not find this parameter to be influential on incremental costs, QALYs or ICERs. The assessment group is correct that UCB did not vary the BASFI progression in patients receiving anti-TNFs; however, the alternative is indirectly tested for its importance to economic outcomes based on the difference in BASFI progression between patients on conventional care and anti-TNFs (the difference is arguably what matters rather than BASFI progression in anti-TNF patients alone) by varying the BASFI progression in the conventional care arm. The results from this sensitivity analysis (UCB original submission, section 11.5.2.1.5, page 175 of) revealed that reducing the difference in BASFI progression between the conventional care and anti-TNFs arms had no significant impact on the base case ICERs.

We therefore ask the assessment group to rephrase their wording to reflect that the assumption of BASFI progression was discussed in the UCB submission and that alternative assumptions were explored.

2.2.3 Data to support the justification of conventional care BASDAI/BASFI assumptions

The assessment group state on page 136 that *"The manufacturer submission assumed no change in BASDAI and BASFI for conventional care during the response period. The manufacturer justified this assumption with reference to evidence from RAPID-axSpA, ATLAS and ABILITY-1 studies, although no specific data were reported to support this."*

UCB notes from our submission that we support our choice of no change in BASDAI and BASFI in patients receiving conventional care on the basis of published literature, as well as evidence from RAPID-axSpA, ATLAS and ABILITY-1.[8, 12, 16-18]

The choice of whether the change in BASDAI/BASFI from baseline is included or not in the model rests on whether the improvement is sustained or transient on conventional care. A sustained (lifelong) response is contrary to Dougados and colleagues who describe conventional care regimens as "palliative at best, providing no alteration of the disease process",[19] and that patients did not achieve minimal clinically important differences for BASDAI or BASFI.[8, 12, 16, 18] Our justification was further supported by data from the RAPID-axSpA study, which had been presented in the clinical section of the submission (UCB submission, Figures 11-8 and 11-9, pages 124 and 125, respectively). However we recognise that this is an assumption in the absence of long-term follow up of patients receiving conventional care. As a consequence we performed sensitivity analysis in which

the conventional care arm does achieve a benefit in terms of BASDAI/BASFI (UCB submission, Section 11.5.2).

UCB would request the assessment group to amend their phrasing to reflect that UCB justification was based on literature in addition to data from RAPID-axSpA. In addition we request that it be noted in the revised phrasing that a sensitivity analysis on this assumption was performed and results provided to the assessment group as part of the original submission.

2.2.4 Radiographic progression in the nr-axSpA population

On page 137, the assessment group state: *"The manufacturer's submission is not explicit about how this additional aspect of progression subsequently alters the BASDAI/BASFI trajectories within the nr-axSpA model….. The justification for this approach and the values subsequently assigned are not formally discussed by the manufacturer and the validity of the approach appears questionable (i.e. given other differences e.g. disease duration, severity of radiographic disease etc, that may differ between the two populations even after radiographic progression has occurred in the nr-axSpA subpopulation)."*

We would like to note that the UCB submission states on page 72 that "*in the base case analysis of the nr-axSpA subpopulation, it is assumed that some nr-axSpA patients may progress to AS during their course of treatment*", which clearly indicates that nr-axSpA patients are converted to AS patients on radiographic progression and would therefore be treated as AS patients in the model. UCB agree however that the impact of this model construct was not addressed. We felt such a discussion was not necessary given the similarities assumed between our nr-axSpA and AS subpopulations in terms of severity ie. utility equation we chose (justified above), radiographic progression ie. its relationship to progression of BASFI and BASDAI, discontinuation rates, etc. (due to a dearth of data on natural history of nr-axSpA patients). Indeed only clinical effectiveness and baseline patient characteristics (and hence mortality due to age differences) were different between the two subpopulations.

UCB would ask the assessment group to recognise that the limited availability of quality data fundamentally limits any model construct. In consideration of this, UCB would request that the assessment group's report be updated to highlight that UCB's model approach was indeed justified; using the best-available evidence from the literature and its RAPID-axSpA trial, which uniquely includes both subpopulations within the same study.

2.2.5 Heterogeneity of study populations in the nr-axSpA analyses

The assessment group states on page 138 that "*Importantly, other manufacturers (Pfizer) argue that the results for certolizumab in this population maybe confounded by population characteristics which could invalidate the indirect comparison of certolizumab versus the other comparator treatments in the current nr-axSpA MTC.*"

As indicated in the original submission (page 55), UCB acknowledges there is a level of clinical heterogeneity across studies identified in the systematic literature review, as it is the case in general in any systematic review. To address the heterogeneity in patient population, the statistical analyses submitted by UCB were performed on AS and nr-axSpA patient subpopulations separately, instead of the entire spectrum of axSpA patients evaluated in the trial. With regards to the nr-axSpA subpopulation, data are only available from three trials, RAPID-axSpA, ABILITY-1 and NCT01258738. There were certain differences in the baseline characteristics of the nr-axSpA patients enrolled in these trials, which need to be taken into consideration when interpreting the results from the pairwise analyses. For instance, all trials had a similar proportion of patients with elevated CRP (30–45%), although the threshold of elevated CRP was not consistent between studies (> 15 mg/L or > 1X ULN or by hsCRP standard). The mean time since symptom onset was slightly shorter in the RAPID-axSpA study (8.1–9.1 years) than the ABILITY-1 trial (10.1 years), whilst the NCT01258738 enrolled patients with dramatically shorter duration of symptoms (2.5 years). Conversely, the ABILITY-1 trial had a shorter average time since disease diagnosis (mean 2–3 years) compared to RAPID-axSpA (mean 4–6 years).

UCB would like to point out that in the nr-axSpA subpopulation, the MTC network of trials used by the assessment group, other manufacturers and UCB are fairly comparable. For instance, while UCB and other manufacturers included three studies (RAPID-axSpA, ABILITY-1 and Dougados 2014), the

assessment group included an additional two studies in their own assessment (Barkham 2009 and Haibel 2008).

As pointed out by the assessment group in their report on page 101, "*For both the AS and nr-axSpA populations the results of the meta-analyses demonstrated that anti-TNFs produce statistically significant and clinically relevant benefits to patients in terms of improving function and reducing disease activity", "Statistical heterogeneity was more apparent in the nr-axSpA analyses than in the AS analyses. This may be due to both clinical heterogeneity in the nr-axSpA trials (such as variation in CRP levels, or the proportion of MRI positive patients), and the fact that fewer studies were available for analysis.", "FDA re-analyses of two key nr-axSpA trials further emphasised the heterogeneity in the nr-axSpA population. Results for an adalimumab trial in nr-axSpA patients suggested reduced efficacy in a centrally diagnosed nr-axSpA population when compared with a locally diagnosed population and that the treatment benefit in the whole trial population may have been driven by benefit in patients who actually had AS, not nr-axSpA. Conversely, in a certolizumab pegol trial which recruited both populations, the efficacy findings were consistent across the AS and nr-axSpA subpopulations, regardless of the discrepancy in local or central pelvic x-ray readings*".

UCB would like to request that the assessment group revises their statement "*invalidate the indirect comparison of certolizumab versus the other comparator treatments in the current nr-axSpA MTC"*, as it is inaccurate to state that the results of the indirect comparison submitted by UCB are invalid, when the exact same studies were compared in other manufacturer submissions and the assessment group's evaluation.

References

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