National Institute for Health and Care Excellence

Multiple Technology Appraisal

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)

AbbVie's Response to the Assessment Report

2 February 2015

Executive Summary

AbbVie welcomes the opportunity to comment on this Assessment Report. We welcome the acknowledgement that non-radiographic axial spondyloarthritis and ankylosing spondyloarthritis are both conditions that have a significant detrimental impact on the quality of life of patients. It is important to acknowledge that the cost effectiveness modelling in the York model does not include the substantial non-NHS costs of AS and nr-axSpA and also does not include the benefits of adalimumab therapy for Extra Articular Manifestations (EAMs) associated with axial SpA. AbbVie considers that these substantial benefits should be taken into due consideration alongside the cost per QALY estimates presented in the Assessment Report and that adalimumab should be recommended for patients with severe AS and nr-axSpA.

AbbVie's comments are grouped into nine sections.

1. AbbVie recommends that caution should be taken in making efficacy conclusions based on the post-hoc non-randomised analyses of a subgroup of patients' radiographs in the ABILITY-I study. Both AS and nr-axSpA patients have similar burden of illness and QoL impairment, and as such the presence or absence of radiographic sacroiliitis sufficient to fulfil the modified New York criteria for AS should not matter as patients with axial SpA deserve appropriate treatment to manage their symptoms and may have a significant burden of disease based on their clinical history, physical examination, and the presence of objective signs of inflammation such as seen on MRI or by elevated CRP.
2. Given the limited numbers of trials available for synthesis in the network meta-analyses for both AS and nr-axSpA, the different populations considered, the differential use of early escape arms, and the relatively small populations in each trial, there is uncertainty regarding the estimates of relative effectiveness obtained in any network meta-analysis conducted in this disease area.
3. AbbVie's economic model and the Assessment Group's modelling of the costs and outcomes have been restricted to improvements in the axial manifestations of AS and nr-axSpA (e.g. BASDAI and BASFI improvements mapped to EQ-5D and treatment costs), excluding any potential cost offsets and quality of life benefits that may arise as a result of improvements in outcomes associated with Extra Articular Manifestations (EAMs).
4. The Assessment Report presents ICERs assuming two different rebound assumptions – rebound equal to gain and rebound equal to natural history. Given, that the actual rebound is likely to be closer to the "rebound to gain" assumption based on clinical opinion, this should give the Appraisal Committee confidence that the anti-TNFs adalimumab, certolizumab, etanercept and golimumab in AS and adalimumab, certolizumab and etanercept in nr-axSpA are a cost-effective use of NHS resources.
5. The York model applies a fixed cost for infliximab based on a mean weight of 73kg and a requirement for 7.4 infusions per year during the maintenance period. The mean cost of infliximab is dependent on the full distribution of AS patients' weight in the UK. The weighted annual maintenance cost of infliximab based on the distribution of patient weight from the ATLAS trial. is £14,323 (not including cost of administration).This is much higher than the £12,429 applied in the York model which does not take into account the mean number of vials required for treating patients across the weight range.
6. AbbVie considers that the York model overestimates the cost of subcutaneous administration with adalimumab. This is because injection training is provided as a free of charge service by AbbVie for patients who have adalimumab delivered to their home.

7. It is important to note the substantial burden that AS and nr-axSpA places on individuals and society. Patients with severe axial spondyloarthritis often have to take early retirement and require support from carers and state disability benefits. The societal impact of AS and nr-axSpA needs to be considered when assessing the cost effectiveness of anti-TNF drugs licensed for these conditions.
8. AbbVie welcomes the acknowledgement in the assessment report that there are data showing the benefits of switching to another anti-TNF in case of treatment failure. The removal of the recommendation not to switch anti-TNF therapy would bring the guidance for AS and non-radiographic axial SpA in line with NICE recommendations for Psoriatic Arthritis, Psoriasis, Crohn's Disease and Ulcerative Colitis, none of which contain a recommendation against switching to a different anti-TNF in case of treatment failure.

Further comments on the assessment report and areas that we consider to be factual inaccuracies or meriting further clarification are outlined in the final section.

1. Classification of patients between AS and non-radiographic axial spondyloarthritis

Section 4.2.2.7 of the Assessment Report discusses the FDA assessment of the ABILITY-1 and RAPID trials, where there were differences in diagnoses arising from x-ray images evaluated centrally, when compared with images being evaluated locally. Section 4.3 which summarises the RCT results, states *"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."*

AbbVie does not agree with this suggestion for a number of reasons explained below. Firstly, the protocol for ABILITY-1 specified that local reading of pelvic x-rays by either a qualified radiologist or rheumatologist would be conducted to determine study eligibility. In addition to their pelvic x-ray results, the rheumatologist assessed a complete set of clinical information on the patient at baseline to make a fully informed diagnosis for study eligibility. Additionally, local readers classified each patient as either fulfilling the radiologic criterion of the modified New York criteria for ankylosing spondylitis (AS) or not, but did not provide a score. Patients who fulfilled the radiologic criterion for AS were screen failed and not enrolled in the study. Therefore, the ABILITY-1 study population reflects non-radiographic axial spondyloarthritis (nr-axSpA) patients who will be treated in clinical practice based on their rheumatologist's diagnosis, which includes a local evaluation of their pelvic x-ray.

The purpose of amending the protocol for ABILITY-1 to include an x-ray at week 104 was to explore possible disease progression from nr-axSpA to AS by local readers. As was done at baseline, at Week 104, local readers classified each patient as either fulfilling the modified New York criteria for AS or not. In addition to the local assessment of the Week 104 x-rays, a post-hoc, non–protocol-specified analysis of these x-rays was conducted using central readers to evaluate potential progression from nr-axSpA to AS.

Central readers were blinded to time point and clinical information and provided a quantitative score for both baseline and Week 104. Central reading of x-rays was not done to evaluate efficacy nor confirm study eligibility. There was no protocol-specified efficacy endpoint to assess the effect of adalimumab on radiographic progression and there was no comparator group. Furthermore, there were no protocol-specified primary or secondary endpoint analyses based on the centrally read baseline classification. Central reading of baseline and Week 104 pelvic x-rays was performed for only 102 out of 185 patients as both time points were required to be available for inclusion in this analysis.

It is important to note that the FDA stated in their briefing book there are significant limitations to their requested post-hoc analysis. Central reading was part of a post hoc analysis that was only applied to a subset of the patient population. The statistical power of the FDA-requested analysis is greatly reduced as it is limited to only 64 centrally-scored nr-axSpA patients (and only 45 in the licensed population) out of 185 patients that were included in the overall efficacy analysis. There are significant limitations to the interpretation of p-values in this situation. Not only are the number of patients in the subgroups very small but there are imbalances in the baseline characteristics between the ADA and PBO arm as well as in the number of adalimumab versus placebo patients.

Baseline comparability of treatment groups achieved by randomisation is not preserved in these centrally-scored subgroups due to differences in baseline demographics and disease activity. For example, among the 38 centrally-scored AS patients there were no clinically meaningful differences in baseline demographics but among patients centrally-scored as nr-

axSpA there was an imbalance in terms of gender distribution, with more males in the adalimumab group compared to placebo; and there was a higher proportion of HLA-B27 positivity in the centrally scored nr-axSpA group, compared to those centrally-scored as AS.

Baseline clinical disease activity was generally similar for both treatment groups in the centrally-scored AS and centrally-scored nr-axSpA subgroups. However, more patients on adalimumab had a positive magnetic resonance imaging (MRI) of the sacroiliac (SI) joints (adalimumab 73% versus placebo 61%) or elevated C-reactive protein (CRP) (adalimumab 67% versus placebo 39%) in the centrally-scored AS subgroup. Since an elevated CRP has been shown to be a predictor of response in axial spondyloarthritis (SpA), this may explain the unusually large response rate noted in this subgroup compared to what has been observed in randomised controlled trials of anti-TNF in AS (73% compared to circa 43% for other anti-TNF AS studies). Similarly, there is an imbalance in these objective measures of inflammation in the centrally-scored nr-axSpA subgroup, with a greater proportion of adalimumab patients having a positive MRI of either the SI joints or spine, but a greater proportion of placebo patients with an elevated CRP at baseline.

In fact, one could argue that if the reduced efficacy results for the centrally read nr-axSpA population are considered valid, which we categorically do not think they are for all the reasons discussed here, then conversely the ASAS40 response rate of 73% vs 17% for adalimumab vs. placebo in the centrally read AS classified patients should also be used as a valid estimate for the efficacy of adalimumab in AS. However, based on the available data of adalimumab and the other anti-TNFs in AS, we know that this is not a typical result and is a vagary of the small numbers and breaking of randomisation for the FDA analysis.

It is well-documented in the literature that significant variability exists in the interpretation of pelvic x-rays. One study showed that of patients classified as AS by a local rheumatologist's read, 11.4% were re-classified as nr-axSpA by central read, and of patients classified as nr-axSpA by a local rheumatologist, 15.5% were re-classified as AS by central read[1]. Central reader interpretation of pelvic x-rays is not necessarily more accurate than the interpretation of local readers and even among expert readers, there is a large inter- and intra-reader variability in the interpretation. Intra-observer agreement is highest for radiographs that are scored at the extremes of the scoring system – grade 0 and 4. However, when the changes are more subtle there is less consistency in how a reader may interpret the same film at two different times with the most common discordance between readers observed in radiographs assessed as grades 1 and 2[2,3].Given that central readers had no access to other clinical characteristics of the individual patients this further highlights the fact that central readers are not necessarily more accurate than local readers and that there is large variability in reader interpretation.

Finally, the Assessment Group note on page 31 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 then established AS*." Given that AS and nr-axSpA have similar burden of illness and QoL impairment, it should not matter whether patients are classified as nr-axSpA or AS according to the presence or absence of radiographic sacroiliitis sufficient to fulfil the modified New York criteria for AS, rather that patients with severe axial SpA encompassing both AS and nr-axSpA receive appropriate treatment with an anti-TNF. The FDA briefing document clearly acknowledges the unmet need in the nr-axSpA population.

In summary, central reading was a post hoc exercise that was not intended to confirm study eligibility. Patients enrolled in ABILITY-1 have nr-axSpA according to the treating rheumatologist as specified in the protocol. Local reading is consistent with clinical practice, and the expected use of adalimumab for this indication. The Assessment Group acknowledges that both AS and nr-axSpA patients have similar burden of illness and QoL impairment, and as such the presence or absence of radiographic sacroiliitis sufficient to

fulfil the modified New York criteria for AS should not matter as patients with axial SpA deserve appropriate treatment to manage their symptoms and may have a significant burden of disease based on their clinical history, physical examination, and the presence of objective signs of inflammation such as seen on MRI or by elevated CRP.

2. Trial selection for evidence synthesis

Given the limited numbers of trials available for synthesis in the network meta-analyses for both AS and nr-axSpA, the different populations considered, the differential use of early escape arms, and the relatively small populations in each trial, there is uncertainty regarding the estimates of relative effectiveness obtained in any network meta-analysis conducted in this disease area. Therefore, AbbVie can understand why the Assessment Group adopted a class effect, based on the best model fit, to model the effectiveness of the anti-TNFs in AS and nr-axSpA. Although the Assessment group do note the various limitations of the data e.g. the large statistical heterogeneity in the nr-axSpA trial populations; AbbVie wanted to point out a couple of issues regarding the trials included in the evidence synthesis and the impact these may have on the estimates of effectiveness.

2.1 Trials included in the evidence synthesis for adalimumab

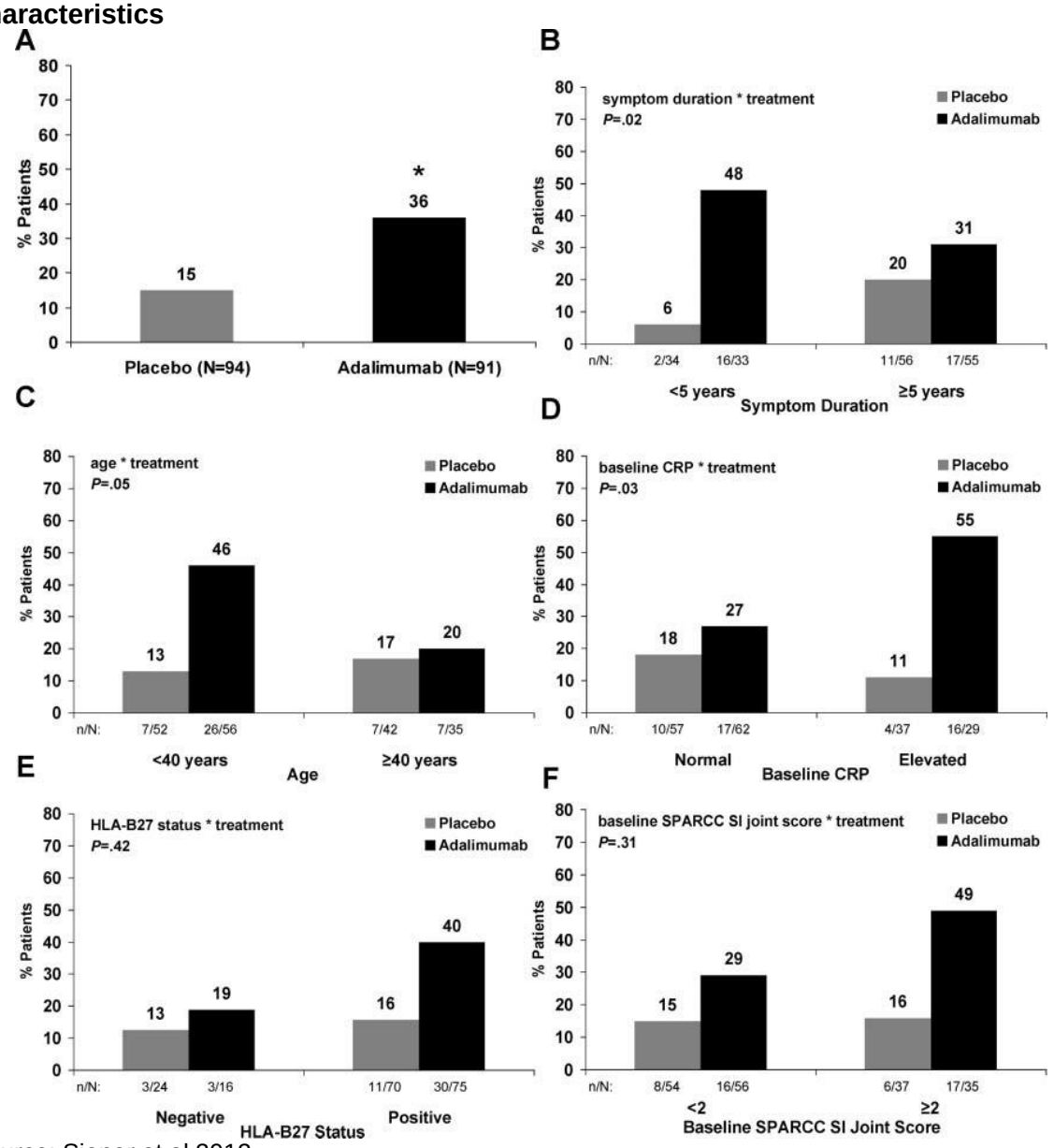
Table 2 of the Assessment Report (page 43) lists the 24 RCTs eligible for inclusion in the network meta-analysis. Whilst AbbVie agrees with the need to include as many trials as possible to strengthen the evidence base linking the network, there are a couple of points about the included trials for adalimumab that may affect the overall estimates of efficacy for adalimumab generated by the Assessment Group (AG).

For ankylosing spondylitis, two Chinese studies of adalimumab have been included – Hu 2012 and Huang 2014. In AbbVie's submission, we also included these trials in the base case but provided a sensitivity analysis with these trials excluded to ascertain the impact of including trials with an entirely Chinese population, which may not be generalizable to results expected in the UK, on the overall efficacy of adalimumab. Hu et al only comprises 46 patients, so its weighted contribution to the pooled estimate of efficacy is quite small. However, Huang et al comprises 344 patients and as such its contribution to the overall estimate is quite strong. In this case, the impact of including Chinese studies in the evidence synthesis was minimal, but AbbVie draws attention to this point because it should not always be the case that all trials are included regardless of the patient population. This is because in some disease areas ethnicity can affect the likelihood of response, and differences between treatments could be inferred that have actually arisen due to differences in the patient populations of the included trials.

For nr-axSpA, the evidence synthesis included two trials for adalimumab – ABILITY-1[4] and a German study by Haibel *et al*. [5] The licence for adalimumab for nr-axSpA is based on a sub-group of patients from ABILITY-1 who have severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (i.e. nr-axSpA) but with <u>objective signs of inflammation by elevated CRP and/or MRI</u>, who have had an inadequate response to, or are intolerant to NSAIDs. Quite rightly, the Assessment Group used the licensed population in the evidence synthesis rather than the full analysis set from ABILITY-1. Conversely, the Haibel study was also included, which covers a much broader patient population than the licence and more importantly is based on eligibility criteria pre-dating the ASAS classification criteria for nr-axSpA. This is an issue because the licence for adalimumab specifically targets a group of nr-axSpA patients who have a greater likelihood of responding to adalimumab treatment. This is evidenced by Seiper *et al* who showed the impact of certain characteristics like age, HLA-B27 status, baseline CRP, baseline sacroiliitis score and symptom duration on the probability of achieving an ASAS40 response (see Figure 1). The inclusion of the Haibel study may therefore underestimate the benefit of adalimumab in nr-

axSpA as the trial population includes a proportion of patients who do not fulfil the ASAS classification criteria for nr-axSpA and/or are outside of the licence for adalimumab.

Figure 1: percentage of patients achieving ASAS40 at week 12 by different patient characteristics



Source; Sieper et al 2012

2.2 Suitability of a network meta-analysis in nr-axSpA

2.2.1 Additional factors contributing to heterogeneity

On page 69 of the Assessment Report, the AG notes that "*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 thresholds, or the proportion of MRI positive patients), and the fact that fewer studies were available for analysis. In light of the statistical heterogeneity across the nr-axSpA trials, both the reliability of the nr-axSpA pooled estimates and their true relevance to patients seen in clinical practice are questionable*."

AbbVie agrees with the Assessment Group that there is considerable heterogeneity and a limited number of trials for nr-axSpA that means that a network meta-analysis in this patient population might not be appropriate.

In addition to the variation in CRP thresholds or the proportion of MRI positive patients already mentioned by the AG, AbbVie wanted to re-iterate that there are additional differences that are known to affect the probability of response. For example, the mean symptom duration of the adalimumab and certolizumab trials is very different, with the adalimumab arm comprising on average patients who have had symptoms of disease for more than double that of the certolizumab trial (see Table 1).

Table 1: Mean symptom duration at baseline from the adalimumab and certolizumab nr-axSpA trials

	Adalimumab – licensed population		**Certolizumab[6]**	
Symptom duration	**ADA 40mg eow (n=68)**	**Placebo (n=72)**	**CTZ 200mg**	**Placebo**
Mean	10.71	10.37	4.8	4.5

This is important to note because Sieper *et al* showed the impact of symptom duration on achieving the primary endpoint ASAS40 (see Figure 1). The percentage of patients achieving an ASAS40 response has been stratified by symptom duration <5 years vs. ≥ 5 years and the data indicate that for patients with symptom duration <5 years 48% patients achieved an ASAS40 response compared to 31% with symptoms for more than 5 years.

If we focus specifically on the licensed population, rather than the full analysis set as was presented in Sieper et al, this difference is more pronounced. Additional analysis undertaken for ASAS40 and BASDAI50 for the licensed population stratified by symptom duration <5 years and ≥ 5 years are shown in Table 2 below:

Table 2: Percentage of ASAS40 and BASDAI 50 responders at week 12 stratified by symptom duration from patients in the ABILITY-1 trial fulfilling the criteria for the licensed population

	Symptom duration < 5 years N=50		**Symptom duration ≥ 5 years N=89**	
	ADA 40mg EOW	**Placebo**	**ADA 40mg EOW**	**Placebo**
ASAS40, %	54.2%	3.9%	34.1%	20.0%
BASDAI50, %	50.0%	0%	34.1%	22.2%

Data from Table 2 clearly show that for patients with <5 years symptom duration prior to initiating adalimumab, there is a much greater likelihood that they will achieve an ASAS40 and/or BASDAI50 response than if they have had disease symptoms for more than 5 years. It is also worth noting that regardless of symptom duration, both groups present a better treatment response with adalimumab use than with placebo.

Given that the average symptom duration in the certolizumab trial was 4.8 years for patients in the CTZ 200mg eow arm with nr-axSpA, and 47.8% of these patients achieved an ASAS40;[7] the fact that 54.2% of patients with symptom duration <5 years receiving 40mg adalimumab eow achieved an ASAS40 response demonstrates the impact this particular patient characteristic has on the likelihood of response.

2.2.2 Classification of nr-axSpA

As already mentioned in Section 2.1 above, the Haibel study includes a proportion of patients who do not fulfil the ASAS criteria for nr-axSpA as the eligibility criteria pre-dates the ASAS classification system. For example, the ASAS criteria require that patients with nr-axSpA are aged below 45 years of age at onset of symptoms, whereas Haibel required that patients were aged below 50 years of age. The population studied might therefore not be representative of patients that would be treated according to the adalimumab licence and as such the inclusion of such a study could be considered irrelevant to the decision problem and may be a contributing factor to the heterogeneity.

The same principle applies to the inclusion of Barkham et al 2009 evaluating infliximab for the treatment of nr-axSpA. Not only was this trial identified as having a high chance of bias by the Assessment Group, but it also predates the ASAS classification criteria and used the Calin criteria to identify eligible patients. The most concerning aspect of this study is that it did not specifically exclude patients that had MRI evidence of sacroiliitis that also fulfils the modified New York criteria for ankylosing spondylitis. Therefore, it is impossible to determine if this is a truly nr-axSpA population or a combination of early AS and nr-axSpA patients. Therefore similarly to Haibel et al, the inclusion of such a study may be a contributing factor to the reported heterogeneity.

2.2.3 Too few trials to perform covariate adjustments

Unfortunately, there are a very limited number of trials in nr-axSpA and the trial populations are relatively small and heterogeneous. As a result it is very difficult to do any sort of covariate adjustment, as the number of coefficients in a model are typically limited by the number of observed data points. Often, a single common coefficient is used to accommodate smaller networks of evidence. In situations with sparse networks like this one, where prior distributions (either informed or uninformed) may dominate, the validity of the network meta-analysis outputs will depend on the validity of prior distribution placed on the co-efficient. Given the fact that the prior distributions could not be based on the data used to inform the posterior distribution, and in the absence of any other data, uninformed priors are commonly used. The problem with this in sparse networks is that the data are less likely to converge. Therefore, whilst covariate adjustment might have helped to deal with the level of heterogeneity reported in the nr-axSpA population, given the network of evidence available for this patient group, AbbVie can completely understand why the Assessment Group were not able to adjust for these differences.

3. Importance of extra-articular manifestations (EAMs) in AS and nr-axSpA

On page 223 of the Assessment Report, the AG notes that "*The long-term impact of anti-TNFs on other important outcomes in AS and nr-axSpA remain uncertain, such as … extra-articular symptoms such as uveitis, inflammatory bowel disease, and psoriasis.*"

Whilst the Assessment Group is right that there are limited data explicitly demonstrating the impact of anti-TNFs on important outcomes such as EAMs, there are some data from open-label trials and registries outlined below that show there is a difference in the effectiveness of the anti-TNF agents under review on the different EAMs associated with axial SpA. Importantly, the Appraisal Committee need to be aware that both AbbVie's economic model and the Assessment Group's model focus specifically on AS and nr-axSpA, as such the costs and benefits have been restricted to improvements in the clinical manifestations of these diseases (e.g. BASDAI and BASFI improvements mapped to EQ-5D), excluding any potential benefits that may arise as a result of improvements in outcomes associated with a given EAM.

EAMs associated with SpA include anterior uveitis (25–30%), psoriasis (10–25%) and inflammatory bowel disease (IBD) (5–10%)[8,9]. As a result, the choice of treatment is

particularly important as the efficacy of the anti-TNF therapies under review varies from agent to agent in the treatment of these EAMs. Furthermore, the 2010 ASAS/ EULAR guidelines state, "The treatment of patients with AS should be tailored according to: the current manifestation of the disease (axial, peripheral, entheseal, extra-articular symptoms and signs)."

The following table highlights the licensed adult indications for all the agents under review in this MTA. As can be seen from Table 3, the anti-TNFs differ in their ability to treat different autoimmune conditions; with adalimumab and infliximab having licences for the most adult indications.

Table 3: Licensed adult indications for the anti-TNFs undergoing this MTA review as of January 2015

Drug	RA	AS	Nr-axSpA	PsA	Ps	CD	UC
Adalimumab	✓	✓	✓	✓	✓	✓	✓
Etanercept	✓	✓	✓	✓	✓	✗	✗
Infliximab	✓	✓	✗	✓	✓	✓	✓
Golimumab	✓	✓	✗	✓	✗	✗	✓
Certolizumab pegol	✓	✓	✓	✓	✗	✗	✗

With regards to data assessing the impact of anti-TNFs on EAMs, for anterior uveitis, Guignard *et al* showed that there was a clear difference between etanercept and the anti-TNF antibodies (infliximab and adalimumab). The incidence of uveitis remained unchanged with etanercept treatment (54.6 vs 58.5/100 patient-years; P=0.92), whereas it was dramatically reduced following anti-TNF antibody treatment (infliximab: 47.4 vs 9.0/100 patient-years; P=0.008, adalimumab: 60.5 vs 0/100 patient-years; P=0.04).[10] Furthermore, data from RHAPSODY and an independent Dutch study by van Denderen and colleagues AS patients with anterior uveitis (AU), showed that adalimumab significantly reduced the number of AU attacks per year. Out of 77 patients enrolled, a total of 52 AU attacks occurred in the year before baseline (68 attacks per 100 patient-yrs.), whereas during adalimumab treatment 19 attacks were observed (14 per 100 patient-yrs.; a reduction rate of 80%). Twenty-six patients with AU in the year before start of adalimumab treatment had recurrent attacks, with a median number of 2.0 AU attacks per year [interquartile range (IQR) 1.00-3.00], whereas during treatment this decreased to 10 patients with a median number of 0.56 attacks per year (IQR 0.30-0.75). Hence, the number of attacks per year decreased by 72% (p = 0.000).[11]

In a published review looking at the therapeutic implications of treating EAMs in SpA, Maghraoui concluded that, "Etanercept appears to have very little effect on inflammatory bowel disease and limited efficacy on the course of uveitis probably inferior to the monoclonal antibodies adalimumab and infliximab." [9]

Like Maghraoui, Van der Horst-Bruinisma *et al* also evaluated the management and evaluation of extra-articular manifestations in spondyloarthritis.[12] The authors found 'in patients with SpA and IBD that the first choice of anti-TNF should be adalimumab or infliximab.'

Data from the RHAPSODY study also provide evidence of the value of adalimumab in treating symptoms of peripheral arthritis and enthesitis in patients with AS[13]. In RHAPSODY adults with active AS (Bath ankylosing spondylitis disease activity index [BASDAI] ≥ 4) received adalimumab 40 mg every other week with standard antirheumatic therapies in a 12-week, open-label study. Effectiveness in enthesitis was assessed using the Maastricht ankylosing spondylitis enthesitis score (MASES, 0-13) and by examining the plantar fascia in

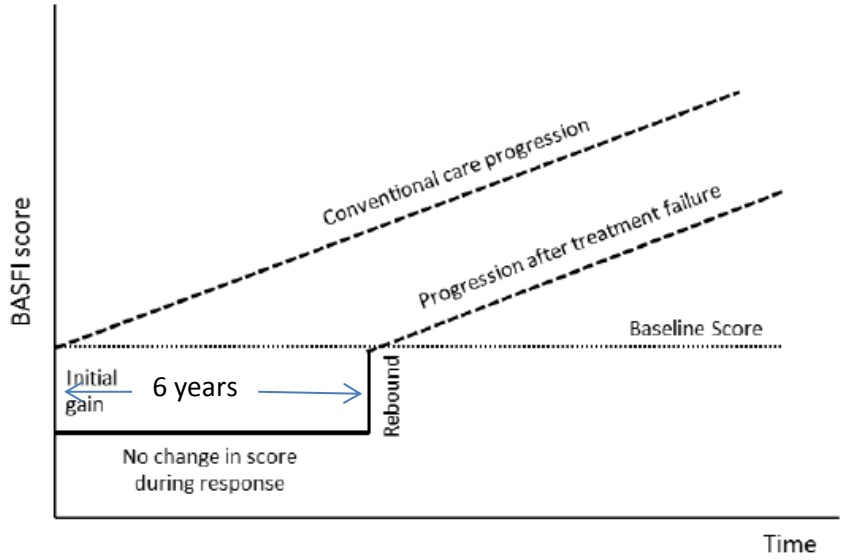
patients with enthesitis (≥ 1 inflamed enthesis) at baseline; effectiveness in peripheral arthritis was evaluated using tender and swollen joint counts (TJC, 0-46; SJC, 0-44) in patients with peripheral arthritis (≥ 1 swollen joint) at baseline. Of 1,250 patients enrolled, 686 had enthesitis and 281 had peripheral arthritis. In 667 patients with MASES ≥ 1 at baseline, the median MASES was reduced from 5 at baseline to 1 at week 12. At week 12, inflammation of the plantar fascia ceased in 122 of 173 patients with inflammation at baseline. The median TJC in 281 patients with SJC ≥ 1 at baseline was reduced from 5 at baseline to 1 at week 12; the median SJC improved from 2 to 0.

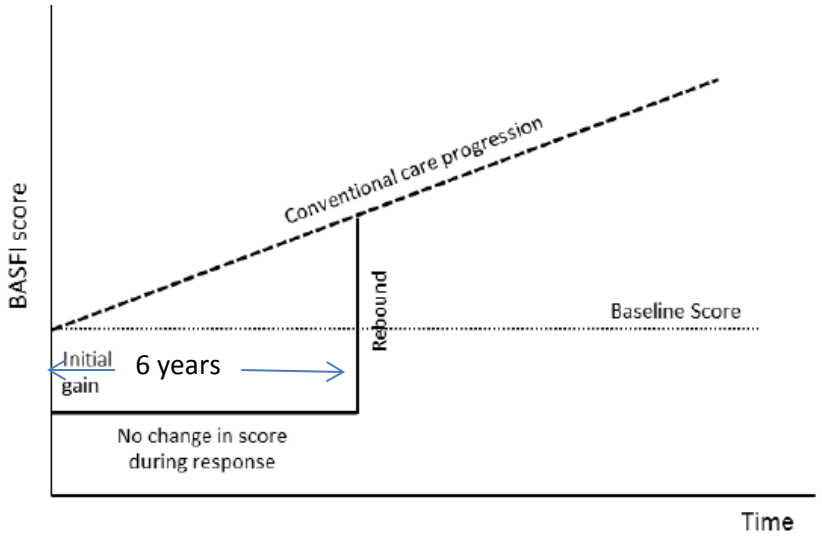
To conclude, whilst limited, there are some published data showing differential benefits between the biologics in the treatment of EAMs associated with axial SpA. Adalimumab has been shown to be efficacious in the treatment of anterior uveitis associated with AS, IBD and psoriasis. As such, the choice of biologic treatment for patients with axial SpA should take into account not only the axial manifestations, but given the high prevalence of uveitis, IBD, psoriasis etc., also take account of any EAM and the benefit different drugs confer on these co-morbidities. Furthermore, it is important to acknowledge that the cost effectiveness modelling does not include the benefits of EAMs in improving the quality of life of patients and reducing NHS costs of treating the EAMs where these are improved by adalimumab therapy.

4. The assumption regarding rebound of BASFI score on stopping therapy

The Assessment Report presents ICERs for the anti-TNFs vs standard care assuming two different rebound assumptions – rebound equal to gain and rebound equal to natural history (Figure 2). The AG notes that, "*in the absence of evidence on the magnitude of any rebound, these alternative scenarios represent 'best-case' and 'worst-case' scenarios possible… the reality regarding rebound is likely to be somewhere between these two scenarios, which should, therefore, be seen as the limits*." In the absence of data to estimate what the exact rebound assumption is, it seems a reasonable assumption that the true rebound lies somewhere between these two scenarios, however AbbVie considers that in reality BASFI rebound is likely to closer to the "rebound to gain" assumption rather than "to natural history." This is because if we consider a patient has been on an anti-TNF agent for 6 years (see Figure 2), the rebound to natural history assumption would conclude that the patient has an instant BASFI worsening on stopping anti TNF therapy equal to the worsening in BASFI over 6 years that would have occurred had the patient been on conventional therapy in addition to the worsening equal to the initial BASFI gain on anti-TNF therapy. If the rebound for patients on long term anti-TNF therapy were of this magnitude the phenomenon of rebound to natural history would have been noted in clinical practice by patients and rheumatologists.

Figure 2: Rebound assumptions used in the Assessment report





It is unlikely that there will ever be any definitive data to be able to determine how BASFI behaves following cessation of an anti-TNF. However, even if we use the AG's defined "worst case scenario" for rebound, the ICERs for adalimumab, certolizumab, etanercept and golimumab in AS and nr-axSpA, are borderline cost-effective according to the York model (circa £33,000). Given, that the actual rebound is likely to be closer to the "rebound to gain" assumption based on clinical opinion, this should give the Appraisal Committee confidence that the anti-TNFs adalimumab, certolizumab, etanercept and golimumab in AS and adalimumab, certolizumab and etanercept in nr-axSpA are a cost-effective use of NHS resources.

5. Costs applied for infliximab in AS

The York model applies a fixed cost for infliximab based on a mean weight of 73kg and a requirement for 7.4 infusions per year during the maintenance period. This equates to an annual maintenance drug acquisition cost of £12,429. It is considered that the use of these two data inputs will provide a lower estimate for the ICER for infliximab for AS than would be likely in UK clinical practice. This is because the mean cost of infliximab is dependent on the full distribution of AS patients' weight in the UK. Applying only a fixed 73kg weight will underestimate the mean cost of infliximab.

This point is illustrated in

Table 4 below, which shows that the weighted annual cost of infliximab based on the distribution of patient weight from the ATLAS trial. The mean drug cost ranges from £12,276.61 assuming 6.5 infusions per year (8 weekly dosing regimen) to £16,368.69 (assuming 8.67 infusions per year (6 weekly dosing regimen). If we assume 7.4 infusions like the York model (50% 6 weekly and 50% 8 weekly), the annual cost of infliximab is £14,322.65 (not including cost of administration).

Table 4: Weighted annual maintenance drug cost of infliximab based on 6 or 8 weekly dosing schedule based on the weight distribution from the ATLAS trial

Weight range from ATLAS study of adalimumab (baseline weight)	% of trial population	No. of vials	Unit cost per vial	Cost per dose	Maintenance drug cost (assuming every 8 weeks dosing schedule)*	Maintenance drug cost (assuming every 6 weeks dosing schedule)*

40kg-60kg	12.7%	3	£419.62	£1,258.86	£8,182.59	£10,909.28
61kg-80kg	39.5%	4	£419.62	£1,678.48	£10,910.12	£14,546.82
81kg-100kg	36.0%	5	£419.62	£2,098.10	£13,637.65	£18,183.52
101kg-120kg	8.6%	6	£419.62	£2,517.72	£16,365.18	£21,820.22
>121kg	3.2%	7	£419.62	£2,937.34	£19,092.71	£25,456.75
Annual drug cost proportional to weight distribution from the ATLAS trial (excluding VAT)					**£12,276.61**	**£16,368.69**

*Drug costs have been calculated including drug wastage for the unused portion of opened vials. This cost is based on 6.5 (8 weekly dosing) and 8.666 (6 weekly dosing) infusions per year which excludes the loading dose cost in year 1. Year one costs would therefore be greater than the costs presented in Table 4 above.

Unfortunately there are limited data to provide the weight distribution for AS patients in the UK which is key for determining the appropriate number of vials and subsequent weighted cost for an AS patient population. However, AS patients are predominantly male as highlighted in the Assessment Report, therefore a weight of 73kg is lower than the mean weight that would be expected assuming a 70:30 male to female split based on available general population weight data.

Furthermore, data from available randomised clinical trials give a mean weight of over 80kg as shown in ATLAS above. It should be noted though that irrespective of what the appropriate mean weight for this patient population is, the analysis using the ATLAS weight distribution illustrates that it is important to consider the distribution of patient weight rather than summary statistics for weight alone when the treatment cost for a population is being calculated. Measures other than the mean cost calculated based on patient weight distribution do not provide information about the cost of treating all patients [14]

The cost applied for infliximab in the York model appears to assume that 50% of patients receive infliximab every 6 weeks and 50% receive it every 8 weeks based on the information in Table 92. However, it is important to note that the pivotal trials for infliximab utilised a maintenance-dosing schedule of infliximab every 6 weeks and as such all the efficacy data are based on this more frequent dosing schedule. Therefore, it is likely that the ICER for infliximab would be higher for AS than per the York model base case, taking into account the patient weight distribution and the 6-weekly scheduled dosing.

6. Cost for administering adalimumab

The York model assumes that all patients receiving an anti-TNF that is administered by subcutaneous injection incur a cost of £49 in their first cycle. We consider that an assumption that all patients receiving adalimumab would incur this cost would be an overestimate. This is because injection training is provided as a free of charge service by AbbVie for patients who have adalimumab delivered to their home.

7. Non-NHS cost burden of AS and nr-axSpA

It is important to note the substantial burden that AS and nr-axSpA places on individuals and society. Patients with severe axial spondyloarthritis often have to take early retirement and require support from carers and state disability benefits. Published evidence on the economic burden of the disease demonstrates that there are substantial costs incurred outside the healthcare system in the form of expenditure incurred by patients and care givers[15]. A study by Bhogal and Kay in Newcastle has provided evidence of a strong relationship between AS severity and receipt of disability benefits[16]. This survey indicated that a BASFI score of greater than 4 is associated with the receipt of disability benefits. A

study by Gunasekera of AS patients in Bath found that the risk of being work disabled increased by 6.6% for each year of diagnostic delay[17]. Therefore, effective early control of disease (as measured by reduction in BASFI score) through the use of anti-TNF drugs could reduce the cost of financial benefit payments for persons with AS and nr-axSpA. The societal impact of AS and nr-axSpA needs to be considered when assessing the cost effectiveness of anti-TNF drugs licensed for these conditions.

8. Benefits of switching to an alternative TNF inhibitor in case of treatment failure

AbbVie welcomes the acknowledgement in the assessment report that there are data showing the benefits of switching to another anti-TNF in case of treatment failure. AbbVie considers that given the typical age of patients starting anti-TNF therapy and the need for lifelong control of their disease it is very important for NICE to permit switching of anti-TNF therapy in case of treatment failure due to loss of efficacy or adverse events. The removal of the recommendation not to switch anti-TNF therapy would bring the guidance for AS and non-radiographic axial SpA in line with NICE recommendations for Psoriatic Arthritis, Psoriasis, Crohn's Disease and Ulcerative Colitis, none of which contain a recommendation against switching to a different anti-TNF in case of treatment failure.

9. Further comments on the assessment report text

The below bulleted points refer to minor comments on some of the text in the Assessment Report:

- Page 24 of the AR, the AG notes that "*patients with nr-axSpA may, or may not, have signs of sacroiliac joint inflammation on an MRI scan*." It is important to note that this is also true for AS patients[18].

- On page 30 of the AR, the AG notes that "*The imaging arm requires evidence of joint damage (erosions or fusion) due to sacroiliitis, either using X-rays (when the disease is classified as AS) or MRI (when the disease is classified as non-radiographic axSpA (nr-axSpA).*This is a close, but not entirely accurate definition, as MRI criteria are used for inflammation only and do not consider chronic changes such as erosions. In addition, MRI does not differentiate between AS and nr-axSpA. These are differentiated only by the presence or absence of radiographic changes.

- On page 30 for clarity it should be noted that to be classified as having axSpA via the clinical arm of the criteria patients are required to be HLA-B27 positive and have at least two of the **other** SpA features.

- On page 30 the statement is made "*An MRI diagnosis may therefore provide the opportunity for treatment to reduce the possibility of long-term structural damage (and associated burden of symptoms)*". This is also true for patients diagnosed via having an elevated CRP and other symptoms which would classify the patient as axial SpA according to the ASAS criteria.

- The duration of the double-blind, placebo-controlled phase for the adalimumab AS trials is listed as 12 weeks in Table 2, page 43 of the AR. However, it should be noted that the randomised, placebo-controlled controlled period in both ATLAS and the Canadian study was actually 24 weeks – but there was an option to escape at week 12, 16 or 20 and receive open-label 40mg adalimumab eow – termed "Early escape Group"

- AbbVie considers it is inappropriate to refer to an "*AS subgroup*" in the ABILITY-1 study. All subjects were enrolled based on the local assessor's opinion that they were non-radiographic axial SpA patients. The central reading was not done to confirm a diagnosis but rather as a post-hoc non-protocol specified evaluation for radiographic progression.

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