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) [ID694]
Pfizer Response to Technology Assessment Report (TAR)
2nd February, 2015

Pfizer welcomes the opportunity to comment on the Technology Assessment Report (TAR) from CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York for the review of Tumour Necrosis Factor (TNF) -alpha inhibitors for ankylosing spondylitis (AS) and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (nr-axSpA) including a review of technology appraisal 143 and technology appraisal 233. The following response is based upon our review of the TAR and the economic model provided to consultees.

Overall, Pfizer feel that the TAR provides a fairly balanced account of the comparative efficacy and safety of anti-TNFs in axial spondyloarthritis (AxSpA). Pfizer agrees with the conclusion in the TAR that "the comparison of ICERs based on the York rebound equal to gain scenario appear broadly consistent with those reported by the manufacturers in both populations." Pfizer believe that, in principle this rebound scenario represents a reasonable base case and welcomes that the Assessment Group (AG) has reached similar conclusions to Pfizer regarding the cost effectiveness of etanercept. Nonetheless, following review of the TAR Pfizer have identified a number of issues with the conditional scores from the synthesis model and with the economic model itself that lead, in some scenarios, to an underestimation of the cost effectiveness of etanercept by the AG. These issues are summarised below and expanded upon further in the main body of our response. To ensure that the TAR includes an accurate representation of cost effectiveness we ask that the model and TAR are updated to reflect our recommendations.

Summary of Pfizer's key points:

1. Clarification is required on the methods and validation of the conditional scores from the synthesis model as these data are new and critical to the conclusions drawn from the cost-effectiveness model.

   Pfizer recommends that the AG describe within the report the validation steps taken for the synthesis model. Pfizer seek confirmation that the conditional scores from the synthesis model are consistent with the population specified in the scope and an explanation of the differences in contingent baselines and outcomes presented in Tables 77 and 82 of the TAR.

2. The baseline BASDAI and BASFI values from the synthesis model for responders and non-responders in AS and nr-axSpA differ to the trial data submitted by manufacturers and are not consistent with the available literature (1). This calls into question the validity of these values and results in a systematic underestimation of the cost effectiveness of etanercept.

Pfizer recommends that the economic model base case should use the weighted average contingent baseline and mean changes that were used in “scenario 2” of the economic model. The AG should not use the data from the synthesis model due to the limitations identified.

3. The AG economic model does not incorporate evidence from open label extension trials that show a continuing improvement in BASDAI/BASFI between week 12 and week 48 for responders to etanercept. As a result, the model underestimates the efficacy and cost effectiveness of etanercept in AS and nr-axSpA.

   Pfizer recommends that the AG economic model is updated to incorporate the continued improvement between 12 weeks and 48 weeks in responders to etanercept.

4. The TAR presents two base case analyses using different BASFI rebound assumptions. Rebound of BASFI to conventional care post-treatment in the “worst-case” scenario modelled by the AG represents an extreme that was agreed as unlikely by clinicians at a Pfizer advisory board. It therefore represents an inappropriate assumption for an AG base case. Furthermore, the “best-case” BASFI rebound assumption in the model is conservative as it does not consider those patients who do not experience full deterioration in function post treatment withdrawal. The instantaneous BASFI rebound assumed by the AG is also unlikely to occur in practice. These assumptions lead to underestimation in both base cases of the cost-effectiveness of etanercept in AS and nr-axSpA.

   Pfizer recommends that a single base case rebound assumption should be modelled. This should reflect a rebound to baseline over a period of 3-6 months. The uncertainty around reasonable upper and lower limits of rebound should be tested in a sensitivity analysis.

5. Trial data demonstrate that BASFI remains stable during prolonged anti-TNF treatment, therefore anti-TNF responders should not experience long term BASFI progression in the AG model.

   Pfizer recommends that the model be updated to reflect no BASFI progression whilst on anti-TNF for both AS and nr-axSpA patients.

6. The AG’s model may underestimate conventional care BASFI progression in nr-axSpA through use of mSASSS to map to progression.

   Pfizer recommends that the nr-axSpA assumption for conventional care progression should be consistent with previous technology appraisals in AS (set to 0.07 per annum) with associated sensitivity analysis.

The six changes outlined above are all of equal importance and should be made to the AG model and TAR so that the economic base case presented more accurately reflects the impact of treating AxSpA with etanercept. Pfizer believes that with these changes the TAR will support the recommendation of etanercept for use in AxSpA. Pfizer believes that etanercept represents value for money for the NHS by delivering considerable quality of life benefits to patients who suffer from a severely debilitating condition.

Pfizer review of the Technology Assessment Report (TAR)

1. **Clarification is required on the methods and validation of the conditional scores from the synthesis model as these data are new and critical to the conclusions drawn from the cost-effectiveness model.**

   In the AG model, BASFI and BASDAI baseline and outcomes contingent on BASDAI50 response were generated using a synthesis model utilising the extended synthesis developed by the AG and additional trial data submitted by manufacturers (see TAR section 6.3). For the purposes of brevity, the source of these contingent data presented in section 6.3 of the TAR will be referred to as the synthesis model throughout this document.

   From reviewing the TAR, it is difficult to validate this approach as two of the tables where these data are presented do not match (namely Tables 77 and 82). Moreover, there is limited description of the steps undertaken by the AG to validate the synthesis model.

   We would suggest that there are three key areas requiring further clarification and additional validation related to the synthesis model and these are summarised as follows:

1.1. The AG report presents two different sets of data from the synthesis model for the AS population (Table 77 and Table 82 of the report). This difference is not discussed in the report, meaning it is impossible to validate this dataset. The values used in the economic model (Table 82) differentially increase the treatment effect for conventional care responders for both BASDAI and BASFI compared with the values presented in the extended synthesis section (Table 77). It is particularly important that the AG clarify the specifics of their approach as these values are used to assess cost effectiveness and may have a profound impact on ICERs.

1.2. The values presented in Table 77 include a baseline BASDAI of less than 4 for the responders of the control population and therefore fall outside of the decision problem for the appraisal.

1.3. The synthesis model assumes a normal distribution for the BASDAI and BASFI baseline scores as well as the change from baseline for placebo (page 175 of the AG report). These are used as a basis to determine the mean baseline BASFI and BASDAI within the responder/non-responder arms. Additional analysis exploring other distributional assumptions (Gamma, log normal etc.) may have increased the fit with the trial data and should be performed to fully understand the limitations of the analysis.

Pfizer recommends that the AG describe within the report the validation steps taken for the synthesis model. Pfizer seek confirmation that the results from the synthesis model are consistent with the population specified in the scope and an explanation of the differences in contingent baselines and outcomes presented in Tables 77 and 82 of the TAR.

2. **The BASDAI and BASFI values for responders and non-responders in AS and nr-axSpA from the synthesis model differ to the trial data submitted by manufacturers and are not consistent with the available literature. This calls into question the validity of the synthesis model and results in a systematic underestimation of the cost effectiveness of etanercept.**

Pfizer questions the extent to which the BASDAI and BASFI values for responders and non-responders from the synthesis model outlined in the TAR (section 6.3) are an accurate representation of these data seen in clinical practice. Pfizer is also concerned about the external validity of the results of the analysis when compared to published clinical trial data. This is a particularly impactful issue as the results are included within the AG's economic model.

In the following section, the results from the synthesis model are compared with the etanercept and adalimumab trial data submitted by manufacturers in Table 1 (nr-axSpA); and etanercept, adalimumab and golimumab in Table 2 (AS). Tables 1 and 2 indicate that there is an important divergence between synthesised and trial data. Our key concerns with the AG approach are summarised in points 2.1 – 2.5 below.

Table 1 A comparison of the synthesised values of BASDAI and BASFI generated by the AG with the trial data from manufacturers in nr-axSpA

			Nr-axSpA					
			control			treatment		
			Synthesised values (Table 83)	ABILITY-1 trial (ADA)	[redacted]	Synthesised values (Table 83)	ABILITY-1 trial (ADA)	[redacted]
BASDAI	**Change in score**	R	-3.34	-3.9	[redacted]	-4.31	-4.79	[redacted]
		NR	-1.06	-0.69	[redacted]	-2.28	-0.55	[redacted]
		R-NR difference	*-2.28*	*-3.21*	[redacted]	*-2.03*	*-4.24*	[redacted]
	Baseline	R	4.54	5.64	[redacted]	5.45	6.21	[redacted]
		NR	6.86	6.46	[redacted]	7.51	6.53	[redacted]
		R-NR difference	***-2.32***	***-0.82***	[redacted]	***-2.06***	***-0.32***	[redacted]
BASFI	**Change in score**	R	-1.88	-2.78	[redacted]	-3.24	-2.75	[redacted]
		NR	-0.05	-0.4	[redacted]	0.08	-0.32	[redacted]
		R-NR difference	*-1.83*	*-2.38*	[redacted]	*-3.32*	*-2.43*	[redacted]
	Baseline	R	2.95	4.37	[redacted]	3.92	3.6	[redacted]
		NR	5.38	4.91	[redacted]	6.04	4.97	[redacted]
		R-NR difference	***-2.43***	***-0.54***	[redacted]	***-2.12***	***-1.37***	[redacted]

R: responder; NR: non-responder; greyed rows indicate difference between responder and non-responder values

Table 2 A comparison of the synthesised values of BASDAI and BASFI generated by the AG with the trial data from manufacturers in AS.

			AS										
			Control					treatment					
			Synthesised values (Table 77)*	Synthesised values (Table 82)*	ATLAS trial (ADA)	GO-RAISE trial (GOL)	[redacted]	Synthesised values (Table 77)*	Synthesised values (Table 82)*	ATLAS trial (ADA)	GO-RAISE trial (GOL)	[redacted]	[redacted]
BASDAI	**Change in score**	R	-2.7	-2.89	-4.5	-4.25	[redacted]	-3.86	-3.86	-4.64	-4.74	[redacted]	[redacted]
		NR	-0.45	-0.36	-0.2	-0.18	[redacted]	-1.73	-1.64	-0.82	-1.22	[redacted]	[redacted]
		R-NR difference	*-2.25*	*-2.53*	*-4.3*	*-4.07*	[redacted]	*-2.13*	*-2.22*	*-3.82*	*-3.52*	[redacted]	[redacted]
	Baseline	R	3.83	4.01	6.31	6.52	[redacted]	4.76	4.8	6.14	6.25	[redacted]	[redacted]
		NR	6.31	6.33	6.37	6.63	[redacted]	7.03	7.08	6.35	6.69	[redacted]	[redacted]
		R-NR difference	***-2.48***	***-2.32***	***-0.06***	***-0.11***	[redacted]	***-2.27***	***-2.28***	***-0.21***	***-0.44***	[redacted]	[redacted]
BASFI	**Change in score**	R	-1.41	-1.72	-2.74	-1.8	[redacted]	-3.02	-3.08	-2.92	-3.03	[redacted]	[redacted]
		NR	-0.17	-0.04	-0.17	0.38	[redacted]	-0.63	-0.44	-0.72	-0.53	[redacted]	[redacted]
		R-NR difference	*-1.24*	*-1.68*	*-2.57*	*-2.18*	[redacted]	*-2.39*	*-2.64*	*-2.2*	*-2.5*	[redacted]	[redacted]
	Baseline	R	3.42	3.52	4.5	3.56	[redacted]	4.17	4.2	4.53	4.45	[redacted]	[redacted]
		NR	5.43	5.46	5.91	5.39	[redacted]	6.02	6.07	5.78	5.48	[redacted]	[redacted]
		R-NR difference	***-2.01***	***-1.94***	***-1.41***	***-1.83***	[redacted]	***-1.85***	***-1.87***	***-1.25***	***-1.03***	[redacted]	[redacted]

R: responder; NR: non-responder; greyed rows indicate difference between responder and non-responder values

*Table 77 are the values from the synthesis model and Table 82 values are the values from the economic model inputs

2.1. The synthesis model predicts lower baseline values for responders compared with non-responders across BASDAI and BASFI outcomes for both AS and nr-axSpA populations (see R-NR difference analyses in Tables 1 and 2, above). The AG offer the rationale that such a result would be expected, as for a given absolute size of BASDAI response, there will be a greater likelihood of achieving a 50% reduction in BASDAI with a lower starting baseline.

This mathematical explanation is not consistent with the definition of response included in the decision problem. A patient is considered to have responded if they demonstrate either a 50% reduction in the BASDAI or show an improvement of 2 BASDAI units. It is therefore the case with patients who have a BASDAI ≥4 that the 2 unit reduction in BASDAI constitutes the smallest change that is required to meet the response criteria. This means that mathematically the likelihood of "response" is not governed by baseline BASDAI.

The predicted BASDAI50 contingent baselines and efficacy estimates made by the synthesis model are also subject to the following limitations:

2.2. In the case of BASFI, the synthesis model over-predicts the magnitude of the differences between responders and non-responders in baseline seen in the trial data (see R-NR difference analysis for responders BASFI baseline marked in bold in Tables 1 and 2).

2.3. In the case of BASDAI, the results of the synthesis model are counter to those seen in trials where responders have a higher baseline BASDAI than non-responders (see R-NR difference analysis for responders BASDAI baseline marked in bold in Tables 1 and 2). This demonstrates a lack of internal validity in the synthesis model.

2.4. The observed differences between baseline BASDAI for responders and non-responders from the synthesis model are also inconsistent with the clinical evidence published in the literature. Arends et al, 2012 (1) have published a review summarising the results from 11 studies in which multivariate regressions were performed to assess the significance of baseline characteristics on BASDAI50 response. Their results demonstrated that achieving a BASDAI50 was associated with a higher baseline BASDAI (2-4). This indicates a potential lack of external validity of the extended synthesis analysis.

2.5. The AG conducted a scenario analysis (scenario 2) in the model (TAR, page 204) using weighted mean values from the trial data submitted by manufacturers instead of the data from the synthesis model. This scenario demonstrates that using the synthesis model data underestimates the cost-effectiveness of anti-TNFs.

The points raised above highlight the issues with using the data from the synthesis model in the economic modelling. The use of patient level data in the Pfizer model to inform contingent baseline values (see Pfizer submission, section 5.2.6), represents an alternative and potentially more accurate approach to that taken. Of the analyses presented by the AG, Pfizer believes that using the weighted means of the trial evidence directly, as in scenario 2 of the economic analysis, would contribute to a base case cost effectiveness estimate that better reflects the trial data than using the synthesis model.

Pfizer recommends that the AG in their economic model base case should use the weighted average contingent baseline and mean changes that were used in "scenario 2" of the economic model.

3. **The AG economic model does not incorporate evidence from open label extension trials that show a continuing improvement in BASDAI/BASFI between week 12 and week 48 for responders to etanercept. As a result, the model underestimates the efficacy and cost effectiveness of etanercept in AS and nr-axSpA.**

   There is evidence suggesting that patients treated with anti-TNFs continue to demonstrate an improvement in their function and disease symptoms after 10-16 weeks, with the full benefit of anti-TNFs not being apparent until after a year as demonstrated in the manufacturer submissions (open label extensions (OLE) of ATLAS, ABILITY1 and GO RAISE pages 129 and 147 of the TAR respectively). For instance, the 311 trial comparing etanercept with PBO in AS patients showed that after 12 weeks of randomised treatment there was an improvement in the etanercept treated patients in BASDAI (baseline: mean 61.0; 12 weeks: mean 33.8). In the follow up open label extension of etanercept treatment (312 trial) it was observed that BASDAI continued to improve and that this was maintained over two years (week 60: mean 21.3; week 108: mean 23.0). The AG model has utilised the treatment effect of anti-TNFs seen in the results of RCTs, but not included any subsequent benefit in patients who continue treatment beyond 10-16 weeks. As a consequence, the cost effectiveness of anti-TNFs, including etanercept, has been underestimated in the model.

Pfizer recommends that the AG model is updated to incorporate the continued improvement between 12 weeks and 48 weeks observed in responders to etanercept.

4. The TAR presents two base case analyses using different BASFI rebound assumptions. Rebound of BASFI to conventional care post-treatment in the "worst-case" scenario modelled by the AG represents an extreme that was agreed as unlikely by clinicians at a Pfizer advisory board. It therefore represents an inappropriate assumption for an AG base case. Furthermore, the "best-case" BASFI rebound assumption in the model is conservative as it does not consider those patients who do not experience full deterioration in function post treatment withdrawal. The instantaneous BASFI rebound assumed by the AG is also unlikely to occur in practice. These assumptions lead to underestimation in both base cases of the cost-effectiveness of etanercept.

The AG presented two rebound scenarios (best and worst-case) on page 184, Section 7.4 of their report, describing the manner in which BASFI deteriorates in anti-TNF responders after discontinuing treatment within the economic model:

(1) BASFI rebounds to anti-TNF responder baseline ("best-case") and

(2) BASFI rebounds back to natural history/conventional care ("worst-case").

In both of these scenarios, as with the etanercept and other manufacturer models, BASDAI is assumed to return to baseline. This is an approach that Pfizer is in agreement with. Comments on the rebound assumption below are restricted to the impact of rebound assumptions on BASFI. In the TAR, it states:

"Given the absence of evidence on rebound, both scenarios (rebound equal to gain and rebound back to natural history) are presented as the 'best-case' and 'worst-case' scenarios possible. In other words, the reality regarding rebound is likely to be somewhere between these two scenarios which should, therefore, be seen as the limits." (page 184, Section 7.4).

However, Pfizer would suggest that fixing the upper and lower estimate of etanercept's cost-effectiveness on these two extreme scenarios is not clinically plausible. We would suggest that return to conventional care as the "worst-case" scenario is too extreme and that the use of the return to baseline as a "best-case" scenario is conservative. In both scenarios it is also assumed that rebound is instantaneous. These assumptions lead to underestimation of the cost-effectiveness of anti-TNFs and are discussed in more detail below.

4.1. The use of 'rebound to conventional care' as a worst-case scenario lacks the clinical validity required to be considered as a reasonable upper limit for rebound and should therefore not be considered as a base-case in the model.

During development of our submission Pfizer sought clinical opinion from an advisory board to determine the likelihood of the rebound to conventional care scenario occurring. This indicated that there is very little published evidence to suggest that function, as measured by BASFI, would deteriorate beyond the levels observed prior to anti-TNF treatment. Applying this scenario in the nr-axSpA population is particularly implausible. The nr-axSpA population is a group of patients who have not yet experienced radiographic progression. Deterioration in function and disease activity will be mediated by the extent of inflammation present. It is therefore unclear

how function (BASFI) could deteriorate to beyond treatment commencement levels if BASDAI does not.

The implications of the 'rebound to conventional care' scenario highlights the lack of clinical validity: an AS or nr-axSpA patient who discontinues anti-TNF treatment after a decade of responding well to therapy will have the same function as a patient that discontinued anti-TNFs treatment at six months and was treated for a subsequent nine and a half years using NSAIDs. The expectation borne from current clinical experience would be that the patient who had a long term response to anti-TNF treatment has been able to control their inflammation more effectively, thus reducing damage and consequent deterioration of function. In the absence of published data the base case should be a return to baseline, chosen based on clinical experience rather than divided between two base case scenarios.

4.2. The use of 'return to baseline' as a best-case scenario excludes the possibility that some patients may have limited post-treatment deterioration.

The AG propose 'rebound to conventional care' as one of the two base cases. However, the possibility that some patients might not rebound as far as baseline (i.e. maintain function after stopping anti-TNF treatment) was given no consideration in the model. This assumption would mean that a patient's BASFI would not increase to their baseline level upon discontinuation. Such a possibility was raised by clinicians consulted by Pfizer on the matter.

It is therefore reasonable to assume that there may be some patients that return to baseline, but also some patients that might not. This important rebound assumption has not been captured in the scenarios put forward by the AG. Pfizer suggests that the use of the 'return to baseline' scenario as a "best-case" scenario is therefore actually a conservative approach likely to underestimate the benefits of anti-TNF treatment received by some patients.

The most reasonable approach to modelling baseline in this case would be to assume that patients return to baseline as the base case and conduct sensitivity analysis within a reasonable range either side of this base case to better reflect uncertainty.

4.3. The assumption of the AG model that rebound is instantaneous underestimates the benefit of anti-TNFs as evidence indicates that rebound can take between three and six months.

In the AG model, it is assumed that upon rebound, there is an immediate return to either baseline (BASDAI and BASFI) or beyond (BASFI). However, the rebound to baseline can often take months as reflected in the assumptions of previous health technology appraisals in AS; for instance in TA233 an assumption of a six month rebound was made (5). The immediate rebound assumption is not supported clinically as described by the Pfizer advisory board, added to which, Baraliakos et al, 2005 provides data on the changes of function and disease activity in patients discontinuing infliximab that had previously been responding to treatment (6). This study showed that the median time for patients to experience a relapse (defined as BASDAI ≥ 4 and physician's global assessment score ≥ 4) was around 14 weeks.

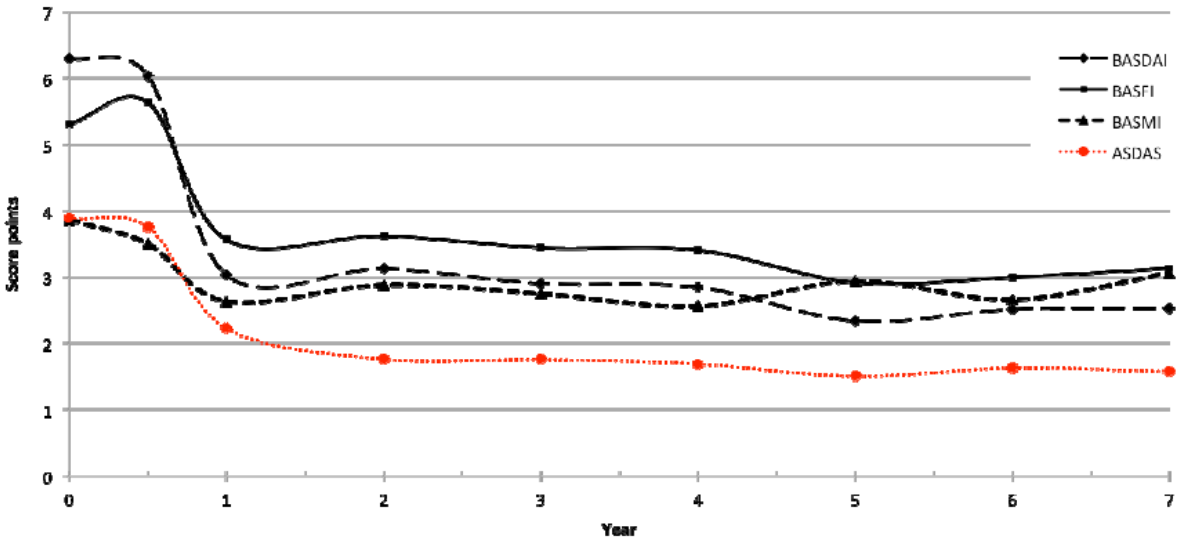
These results indicate that the instantaneous change in BASDAI and BASFI assumed by the AG is a conservative assumption and is likely to underestimate the actual benefit received by patients.

Pfizer recommends that a single base case rebound assumption should be modelled. This should reflect a rebound to baseline over a period of 3-6 months. The uncertainty around reasonable upper and lower limits of rebound should be tested in a sensitivity analysis.

5. **Trial data demonstrate that BASFI remains stable during prolonged anti-TNF treatment, therefore anti-TNF responders should not experience long term BASFI progression in the AG model.**

Baraliakos et al 2013 (7) report outcomes of AS patients during continuous 7 year treatment with etanercept. These data, although based on a limited number of subjects, suggest no notable increase in BASFI over seven years for patients who respond to anti-TNF treatment. Rather than relying on proxy measures of function such as mSASSS, that have limited validity for the nr-axSpA population, these trial data should be used to inform the long-term progression rate of AS and nr-axSpA patients receiving anti-TNF treatment in the AG model. The use of indirectly calculated treatment effect from conventional care BASFI progression based on modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) instead of trial data disadvantages the anti-TNF treatments by assuming progression when there is none.

Figure 1: Course of disease related clinical parameters reproduced from Baraliakos et al 2013



Pfizer recommends that the model be updated to reflect no BASFI progression whilst on an anti-TNF such as etanercept for both AS and nr-axSpA.

6. **The AG's model may underestimate conventional care BASFI progression in nr-axSpA through use of mSASSS to map to progression.**

The mSASSS score (0-72) system is used for scoring chronic changes on X-rays in the cervical and lumbar spine in clinical trials. Such radiographic changes in the spine are generally only seen in advanced stages of AxSpA. It is reported that patients generally progress from magnetic resonance imaging (MRI) sacroiliac joint (SIJ) negative to MRI SIJ positive then on to X-ray sacroiliitis positive, and only then do some patients advance further to sacroiliitis and/or spine X-ray positive (8). The nr-AxSpA population are, by definition, patients whose disease has not progressed to the point where radiographic changes can be detected in the SIJ, and therefore these patients would not generally be expected to demonstrate any radiographic changes in the spine that would be registered in the mSASSS score (a very low mSASSS score has been observed in some nr-axSpA patients in large cohorts (9)). In nr-axSpA patients, deterioration of function whilst on conventional care is likely to be related to inflammation rather than radiographic changes in the spine. Therefore the use of the mSASSS score in the AG model to predict BASFI progression in nr-axSpA population is not as relevant as it is in AS and may underestimate the progression of BASFI in nr-axSpA patients. Previously accepted assumptions for BASFI progression, such as 0.07 per annum in TA233 andTA143 would provide a more realistic base case progression rate.

Pfizer recommends that the nr-axSpA assumption for conventional care progression should be consistent with previous technology appraisals (eg TA233) in AS (set to 0.07 per annum) with associated sensitivity analysis.

References

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Factual inaccuracies and other points

TAR report location	Pfizer comment and action
Table 79 (page 178)	This table contains information marked as confidential; however, it is not clear if this is deliberate. The information used for the model inputs, which presumably reflect the data derived from the extended synthesis are available in Table 83.
Table 80 (page 178)	In the footnote Table 80, (Conditional scores observed in trials in nr-axSpA) the AG make the comment: "*Pfizer only reported results for ETN 50 mg*" This comment could be misinterpreted as results for doses other than ETN 50 mg were not provided by Pfizer; however the 1031 trial only included the ETN 50 mg dose. We therefore request that the above text is changed to: "*Trial 1031 only included ETN at 50 mg once weekly dose*"