Pfizer response to the Appraisal Consultation Document for TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (including a review of TA143 and TA233) [ID 694].

Pfizer would like to thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. We welcome the interim recommendations and are pleased that the Committee has concluded that etanercept is considered a cost effective use of NHS resources in both indications.

Pfizer agree with the Committee's conclusions regarding the validity of key assumptions used in the Assessment Group's economic analysis:

- That it is more clinically plausible that patients who stop treatment with TNF-alpha inhibitors have a BASFI that rebounds to baseline score rather than to a poorer state of health than they were at baseline (Section 4.63, page 51).
- That there is no evidence to support the implications of the Assessment Group's evidence synthesis used in the base case economic model, ie that patients with more severe disease will be less likely to experience a clinically meaningful benefit than patients with less severe disease (Section 4.61, page 50).

Pfizer believe that the combination of the assumptions of a return to baseline and the use of the trial subgroup analyses submitted by the manufacturers (scenario 2) provide the clinically most plausible ICERs from the Assessment Group's economic analysis.

We summarise below several points of factual accuracy relating to the interpretation of the analysis on sequential use of TNF-alpha inhibitors. We believe that this analysis submitted by Pfizer (where all patients that withdraw from treatment, whether due to intolerance or loss of efficacy, are entitled to a second line TNF-alpha inhibitor) may have been misinterpreted in the ACD. Section 4.69 (page 55) summarises that the Assessment Group did not consider the analysis as valid as there is only a £1,000 increase in the ICER for sequential treatment when there is a 30% reduction in efficacy for second line treatment. The implication of this is that the Assessment Group would expect a 30% increase in the ICER (which would be greater than £1,000). In order to ensure that the ACD is factually accurate, Pfizer would like to provide some clarification on how the analysis was performed.

1. In Pfizer's sequential treatment sensitivity analysis, the second line treatment is selected at random from a range of licensed TNF-alpha inhibitors that excludes the specified first-line treatment. This means that the model compares sequential

treatment pathways and not specified, second line treatments. Consequently the relationship between second line efficacy and the cost effectiveness of a sequential pathway compared to a standard treatment pathway is non-linear. In our base case analysis patients only receive second line treatment if they achieve a BASDAI 50 response at 12 weeks with first line treatment, but discontinue due to intolerance. The sequential treatment sensitivity analysis also allows those patients who discontinue due to loss of efficacy to commence a second line TNF-alpha inhibitor (see Figure 1 below). The probability of a patient both achieving a BASDAI 50 response at 12 weeks and subsequently discontinuing due to loss of efficacy is relatively low and hence few additional patients receive second line TNF-alpha inhibitor treatment in the sensitivity analysis, limiting the impact upon the ICER.

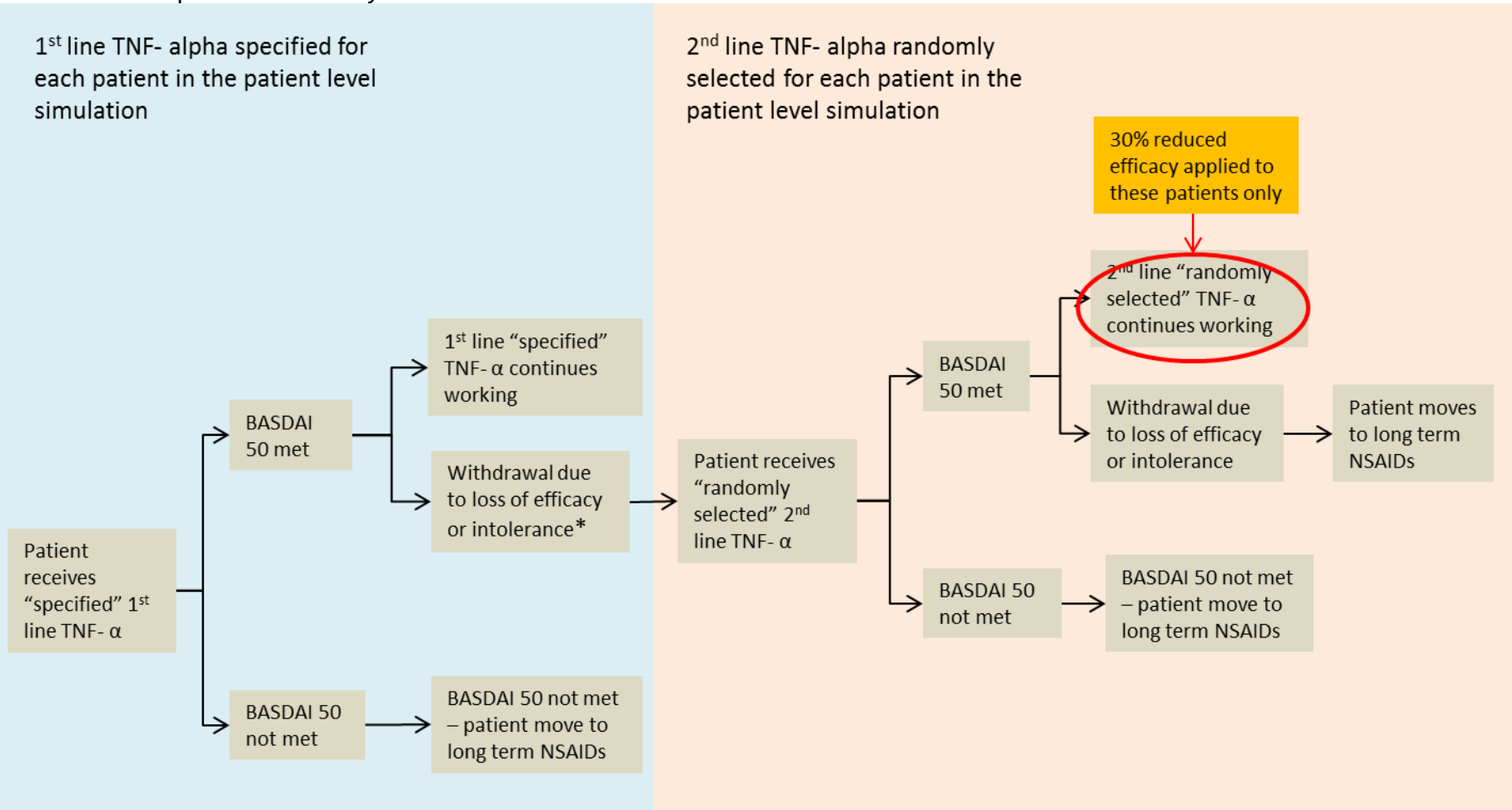
2. The ACD states in Section 4.32 (page 32):
"The ICER for infliximab as a second treatment was £35,840 per QALY (lower than the ICER for infliximab as a first treatment)."

This interpretation is incorrect; as explained in point 1, infliximab is not expressly analysed as a second line treatment. The sequential treatment infliximab sensitivity analysis has a lower ICER than the base case because more patients go on to receive the second line TNF-alpha inhibitor, which provides benefit at lower cost than infliximab (which is the highest cost TNF-alpha inhibitor) thus making the whole pathway more cost effective. Pfizer suggest that the ACD is updated to reflect the correct interpretation as follows: the ICER for infliximab as part of a treatment sequence that allows second line treatment after discontinuation due to intolerance or loss of efficacy was £35,840 per QALY (lower than the ICER for infliximab as part of a treatment sequence where second line treatment is only allowed with discontinuation due to adverse events).

As a consequence of the points raised in 1.1 and 1.2, Pfizer also suggests deletion of the sentence in section 4.69 (page 55):
"*The Committee noted that the Assessment Group did not consider this analysis valid*."

In conclusion, Pfizer welcomes the interim decision of the Appraisal Committee and believe this represents a step forward in the clinical management of patients across the spectrum of axial spondyloarthritis.

Figure 1. Flow of patients through the Pfizer patient level simulation model in the sequential use sensitivity analysis demonstrating the non-linear relationship between efficacy and outcome.



*In the base case, patients may only progress to second line TNF-alpha if they withdraw due to intolerance, the diagram presented here is the sensitivity analysis where patients receive second line TNF-alpha therapy whether they withdraw due to intolerance or loss of efficacy.