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National Institute for Health and Care Excellence

Multiple Technology Appraisal

Arthritis (juvenile idiopathic) - abatacept, adalimumab, etanercept and tocilizumab (including review TA35) [ID783]

AbbVie's Response to the Assessment Report

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Executive Summary

AbbVie welcomes the opportunity to comment on the Assessment Report for the multiple technology appraisal of abatacept, adalimumab, etanercept and tocilizumab for juvenile idiopathic arthritis (JIA).

AbbVie considers that patients should have access to these treatments given the long term progressive nature of the disease and the patient group affected and we are concerned that the incremental cost-effectiveness ratios (ICERs) reported in the Assessment Report does not show the true value of biologics and that the Committee may make a decision based on a number of limitations with the economic evaluation.

AbbVie agrees with the Assessment Group that their model has limitations and accepts that this is mainly due to the paucity of evidence**. We do however believe that there are a number of assumptions within the model that result in an ICER for biologic therapies (and adalimumab in particular) that can only be considered conservative.**

Our concerns are outlined briefly below, and discussed in full in Section 1 under the subsections indicated. The remainder of the document is structured into Section 2 - points of clarification and Section 3 - factual inaccuracies.

Key points and concern with the Assessment Report and modelling

1.1 AbbVie considers that the **wider societal benefits need to be considered as part of an overall value judgement** when appraising the biologics in this MTA. AbbVie believes that only a partial view of the true cost-effectiveness of treatments will be attained if these benefits are not incorporated in the economic evaluation.

1.2 **Benefits of adalimumab on juvenile idiopathic arthritis associated uveitis (JIA-U) have not been incorporated**, although there is evidence suggesting efficacy with adalimumab. As result, the potential cost savings and improved quality of life for those patients with JIA-U using adalimumab are not reflected in the current adalimumab ICER.

1.3 The **benefits of biologics during the first three months of treatment** have not been accounted for. This conservative assumption negatively affects the ICERs for biologics.

1.4 The **resource use with methotrexate may have been underestimated** and **utilities overestimated** because **the long-term impact on disease progression has not been incorporated**. In particular, the economic evaluation does not take into account the **cost or utilities of joint surgery or visual impairment due to JIA-U**. Additionally, **disutilities of surgery and surgery-related complications are not considered.** Other areas of concern are the assumptions that there is **no differentiation between resource use in the biologic and methotrexate arms**, **patients stopping treatment are assumed to incur the same medical resource costs as patients on treatment** and **adverse events incur cost but not disutilities**. It is also unclear to AbbVie how the **cost of disease flare** was calculated and we believe that this **may have been underestimated considerably**. All these issues disproportionately favour the methotrexate cohort in the model.

1.5 AbbVie considers that there are **difficulties in conducting an indirect comparison** in this disease area which makes the results highly uncertain and limits the conclusions that can be drawn from the adjusted indirect comparison. Specifically, the definitions of **disease flare** differed between the studies and this does not allow for firm conclusions to be drawn between, for example adalimumab and etanercept, because adalimumab had a more stringent requirement for disease flare. **Calibration of the 'placebo' arms** to establish a reference arm for the calculations of relative effectiveness is also difficult because the placebo arms are not representative of a true placebo response because patients may or may not have the option to take methotrexate in the trials included in the indirect comparison.

AbbVie trusts the Committee will take these points into consideration at the Appraisal Committee meeting in September.

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Section 1. Comments on assumptions in the Assessment Group Report and Model

1.1 Wider societal benefits need to be considered as part of an overall value judgement

As the Committee is aware, cost–utility analysis cannot be the sole basis for NICE's decisions and committees should use their judgement about the acceptability of an intervention as an effective use of NHS resources taking into account amongst others, the social value thereof.

AbbVie therefore welcomes the acknowledgement in the Assessment report that there are other factors relevant to the NHS and other parties that can have a significant effect on the lives of patients and their family (Section 6 of the report). The report identifies factors directly impacting children and young people such as educational attainment; ability to gain employment in adulthood; social and leisure activities and sport; and impact on parents and caregivers such as their employment and income. The report states that the effect of these may create or widen socio-economic and health inequalities in this group of patients.

Additionally, when considering the burden of illness to the healthcare system and society the evidence suggest that JIA treatment is substantial, with indirect costs forming a sizeable part of that cost. Whilst these costs is may be difficult to quantify, a systematic review published in July 2015 showed that the annual total cost per patient could be as high as €30,000/patient (2010 cost year), of which indirect costs, attributed to loss of income for parents, were between 6% and 28% of direct cost in the last decade.[1]

As there is limited data on these factors and the costs thereof are not directly covered by the NHS, AbbVie understands that it would not be possible to incorporate them fully into an economic model. However, as shown with the scenario analysis that incorporated a disutility for patient caregivers, factoring in one such element improves the cost-effectiveness for the biologic treatments under review. Nonetheless, AbbVie believes that the incorporated caregiver burden is only a conservative estimate as the evidence from published literature also indicate towards significant burden of JIA on parents work productivity. For instance, a recent study representing 3,528 JIA cases in USA concluded that parents having a child with JIA were 2.78 times (95% CI=1.47 to 5.26) more likely to report work-time loss compared to parents having no child with JIA[2].

It is therefore likely that incorporating indirect costs such as welfare benefits that provide financial support for patients with functional impairment, loss of income due to sick leave or attendance at rheumatology clinics for parents or patients of working age and loss of productivity for parents or patients of working age would further improve the cost-effectiveness of biologics. To this point, the systematic review by Angelis et al.[1] found that the introduction of new therapies such as biologics substantially decreased indirect costs. This finding is not surprising if taking into account that costs were substantially skewed towards patients not in remission, and the authors hypothesise that this is due to the availability of biologics, which provide improved efficacy over existing treatments.

AbbVie therefore believes that an economic evaluation where these factors are not considered gives only a partial view of the true cost-effectiveness estimates of treatments and we therefore request that the committee give consideration to the evidence regarding wider societal benefits in patients with JIA.

1.2 Benefits of adalimumab on juvenile idiopathic arthritis associated uveitis (JIA-U)

AbbVie wishes to emphasise the point in the Assessment Report that adalimumab will be more cost-effective in JIA patients if it is assumed that adding vision loss, which is associated with JIA-U (which is an extra-articular manifestation of JIA and not a separate group of patients with JIA), will decrease patient quality of life due to advancing JIA and likewise for JIA-U patients refractory to methotrexate. This is not an unreasonable assumption to make and is one which has been accepted in other appraisals where vision loss is considered as an outcome[3,4,5,6,7,8]

Also, whilst we welcome the acknowledgement in the report that adalimumab has shown efficacy in these patients, we are disappointed that this could not be explored further in the economic modelling. Understandably, the lack of randomised controlled trial (RCT) data was the reason for this, but AbbVie would like to point out that it may have been instructive to assess the outcomes in these patients using the body of evidence from observational studies and registries. As stated in the report, the evidence from these studies appears to indicate that adalimumab is associated with improvements in intraocular inflammation and visual acuity, and a decrease in the use of corticosteroids. It is also noted that the SYCAMORE trial, which is a RCT funded by the NIHR HTA programme and Arthritis Research UK, has closed early for recruitment following an interim analysis showing a favourable effect for adalimumab.

As outlined in the AbbVie submission, the costs associated with uveitis in children in unknown, but a review of NICE technology appraisals found the cost of visual impairment and blindness in adults have been estimated to be between £585[9] to £17,300[10] per year, with most NICE appraisals incorporating visual impairment or blindness using an annual cost of approximately £6,000.[11,12,13,14] This does not take into consideration the cost of surgical procedures such as glaucoma which can range from £1,257 to £2,355 or cataracts which can range from £1,233 to £2,381[15], just to mention two complications. Ocular surgery rates for glaucoma and cataracts in JIA patients with uveitis have been found to range from 9% to 65% depending on the follow up time of the study[16,17].

The potential cost savings and improved quality of life for those patients with JIA-U using adalimumab are not reflected in the current ICER and we hope that the Committee will not dismiss the effect of adalimumab on JIA-U based on the prior lack of RCT data, but will consider the growing body of observational studies and registry datasets as a valid and useful source of evidence underpinned by the favourable primary efficacy endpoint from the recently completed SYCAMORE RCT.

1.3 Utility gain with the biologics

It is assumed in the model that there is no utility gain during the first 3 months for biolgoics, based on the publication by Prince et al. AbbVie believes this is an unreasonable assumption which biases against biologics.

Prince et al. evaluated the utilities at baseline (month 0), after month 3, 15 and 27. The Assessment Group Assumed that the utility measured after 3 months by Prince et al. only starts in the second cycle i.e months 4-6. It is plausible that patients would experience some benefit during the first 3 months otherwise they would not have showed an improved utility value in the study by Prince et al. (from 0.53 at month 0 to 0.69 after 3 months). Should the concern be that this effect does not occur right at the start of the model, this can be accounted for by using a half-cycle correction, which is

currently not applied in the model. Similarly, the utility gains seen at month 15 and 27 in the study are only applied at months 18 and 30, respectively. Again it is not unreasonable to expect that the benefits seen at the end of months 15 and 27 in the study would have occurred at some point prior to months 15 and 27, and AbbVie's suggestion would be to apply these utility values in the cycle prior to months 15 and 27 i.e. months 13-15 and 24-26.

AbbVie therefore requests the utility gain with biologics be amended in the model to better reflect the benefits thereof. This will give a better indication of the QALY gains with biologics and a better reflect the true value of the biologics.

1.4 Assumptions on resource use and outcomes with methotrexate

AbbVie believes that the assumptions for resource use and outcomes have underestimated the cost and overestimated the utilities with methotrexate, resulting in an ICER that favours methotrexate over biologics. These assumptions are influenced by the lack of data on long-term disease outcomes which meant these outcomes could not be modelled, but it is also influenced by assumptions on the outcomes with adverse events, cost of disease flares and lack of differentiation on resource use between biologics and methotrexate.

AbbVie would request the Committee bear these points in mind when deliberating on the most plausible ICERs for the biologics under review.

1.4.1 Long-term disease progression with biologics and methotrexate

As acknowledged in the Assessment Report, the long-term impact of disease progression has not been incorporated into the cost-effectiveness analysis, and in the case where it can be shown that biologics reduce long-term damage compared to treatment with methotrexate, the biologics would be more cost-effective.

AbbVie understands that there is a lack of long-term data for the biologics compared to methotrexate, but we believe that, based on the effects of anti-TNFs on long-term disease progression on other arthritic inflammatory conditions such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis, it is not unreasonable to propose that patients with JIA could also see a positive effect when taking anti-TNFs such as adalimumab, and that this effect will be better than with methotrexate, particularly in a population that has failed to respond to methotrexate but continue to use it.

Should it be accepted that biologics are more effective at reducing long-term damage compared to methotrexate, then the cost consequences of treating with methotrexate will be higher and the outcomes worse than what the current ICER reflects. The points below expand on this.

1.4.1.1 Cost associated with the long-term impact of disease progression

Long term data on outcomes are limited, but in a study in 261 adults with JIA in the UK prior to the era of biologics, continuing active disease over long periods was identified as one of the predisposing factors for surgery ($p<0.001$). The authors concluded that disability levels were often related to continuing active disease over long periods.[18] More recently, Elhai et al. concluded that structural peripheral damage is frequent in young adults with polyarticular JIA and correlated with a more severe disease[19].

This is particularly important as the consequence of disability and structural damage is surgery or in some patents, visual impairment due to JIA-U. Surgery rates in JIA vary and depend on the duration of the studies' observation periods, nonetheless, the literature reports rates of 7% to 28% for joint surgery[20,21] and 9% to 65% for ocular surgery[22,23]. The higher rates reflect the occurrence of revision joint surgery to remove old implants and replace them with new components later in life or repeat glaucoma / cataract surgery.

The cost of such procedures may be significant – for example, the cost of an artificial adult hip ranges from £1,557 to £3,869[24], with the cost to the NHS for the procedure ranging from £6,023 to £9,945[25]. As mentioned in Section 1.2 of this document, the annual cost of visual impairment and blindness in adults are substantial and additionally, does not take into consideration the cost of surgical procedures such as glaucoma or cataracts, to name just two procedures.

The current ICERs do not take these costs into consideration and does therefore not provide a full picture of biologics' cost-effectiveness. Adalimumab in particular is disadvantaged by this approach.

1.4.1.2 Utilities associated with the long-term impact of disease progression

As noted in the Assessment Report, a constant utility was assumed with methotrexate, which would favour this treatment if patients do experience disease progression whilst on methotrexate.

Additionally, disutilities of surgery or surgery-related complications are not considered in the economic evaluation and are not discussed in the report. Joint surgeries are not only associated with increased mortality risk, but may also result in complications such as persistent pain, periprosthetic infection, intraoperative bone fractures, mechanical failure and nerve injury that require further medical management.[26,27,28,29] Complications related to ocular surgery may include fibrin formation resulting in synechiae formation (an eye condition where the iris adheres either to the cornea or lens), pupillary membrane formation, hypotony, secondary cataract formation, inflammation and glaucoma, all of which require further management.[30,31]

Disutilities with surgery would be temporary, but surgery-related complications with associated Disutilities would be temporary in most cases and permanent in many cases. Similarly with JIA-U, visual impairment would be temporary, however, if left untreated, JIA-U could cause permanent damage resulting in a permanent lower health state.

As result of not considering lower utilities for patients undergoing surgery, experiencing surgery-complications or visual loss, the current ICERs should be considered conservative. Again, this is particularly true for adalimumab.

1.4.2 Differentiation between resource use in the biologic and methotrexate arms

Whilst it is not explicitly stated in the model, the population under evaluation are patients who have previously failed treatment (as per the biologics' licenced indications), and as such it seems counterintuitive to assume that the same resources will be used in a population who continue on a failed treatment such as methotrexate, and patients who are on one of the biologics for the first time. And although it is noted in the report that the clinical experts consulted by the Assessment Group did not comment that there would be <u>no</u> difference between monitoring patients on methotrexate and biologics, they did comment that the resources for monitoring patients were <u>not</u>

substantially different between the patients treated with methotrexate only or with a biologic. This would imply that there would be some difference and AbbVie believes this difference would be in favour of the biologics as these treatments offer better disease control than methotrexate, and patients who remain on failed treatment would be reasonably be expected to require more resources. Indeed, the publication by Prince et al., used for the utility values in the model, found that resource use was higher prior to the start of etanercept than after the start thereof. It is noted that the 100% of patients on the registry were on methotrexate prior to the start of etanercept, thus supporting our suggestion that there would be a difference between patients who remain on methotrexate and patients on biologics.

The assumption that the same resources are used in the treatment arms should be further explored with clinical experts and if necessary, amended as it may not be reflective of clinical practice and negatively affect the biologics' cost-effectiveness.

1.4.3 Resource use 'off treatment'

The model assumes that once patients stop their treatment, they will be in the 'off treatment' arm of the model and will incur the cost of GP visits, hospital appointments and hospital tests. For the methotrexate cohort, it assumes that patients will not be receiving any drug treatment for their disease, whilst for the biologics it is assumed that patients will receive methotrexate.

AbbVie believes this is an unreasonable assumption which unduly favours the methotrexate cohort. In clinical practice patients would not be left without any treatment once they stop methotrexate and would at the very least, receive high or low dose steroids, non-steroidal anti-inflammatories (NSAIDs) or other disease modifying drugs such as sulfasalazine, hydroxycholorquine and leflunomide[32].

This assumption should also be explored with clinical exports and if necessary, the cost of these treatments should be added to the methotrexate cohort in order to fully evaluate the cost-effectiveness of biologics.

1.4.4 Outcomes of adverse events

Whilst the cost of treating adverse events for the treatments under review has been incorporated, no disutilities for adverse events have been incorporated. It would be expected that, similar to the disease flare disutility, adverse events would have an associated disutility. Although it would not be expected to be a key driver for cost-effectiveness, the ICER for the biologic treatments compared to methotrexate would improve as methotrexate is associated with small, higher adverse event rates in the model.

1.4.5 Source of disease flare cost and assumptions on resource use during disease flare

It is not clear from the report or the model which currency code and description in the National Schedule of Reference Cost was used for the cost of disease flare (see Section 5.6.1 Data sources – Resource use, p128). A search through the reference cited could not find the cost used in the model (£429.97). AbbVie considers that the most likely currency codes and descriptions would be *PH34D: Paediatric Musculoskeletal or Connective Tissue Disorders, with CC Score 0, HB25J: Knee Procedures for Non-Trauma, Category 1, 18 years and under, without CC* or *HB99Z: Other Procedures for Non-Trauma*. Both the report and model describes the treatment as "inpatient", therefore the categories

could be *elective inpatients*, *non-elective inpatients-long stay* or *non-elective inpatients-short stay*. AbbVie has been advised that it could also be considered a Day Case. The treatment costs are summarised in **Table 1** below.

Table 1. Costs for the Health Resource Group currency codes considered most appropriate for treating disease flares[33].

HRG currency code and description	Elective inpatients	Non-elective inpatients-long stay	Non-elective inpatients-short stay	Day Case
PH34D: Paediatric Musculoskeletal or Connective Tissue Disorders, with CC Score 0	£1,438	£1,740	£515	£516
HB25J: Knee Procedures for Non-Trauma, Category 1, 18 years and under, without CC	£2,034	£2,972	£536	£1,528
HB99Z: Other Procedures for Non-Trauma	£3,588	£5,420	£1,335	£939

Additionally, it should be noted that only one cost is applied in the model. This would be reasonable for when attending the clinic once a flare is experienced in order for the diagnosis to be confirmed and treatment options determined. However, a subsequent visit would be required to administer treatments such as intra-articular steroids – it does not appear that this additional visit and cost has been factored into the model. A subsequent cost for attendance at the clinic would also need to include the cost of intra-articular steroid injections in addition to the clinic visit in the same way that intravenously administered biologic drug costs are considered additional to a clinic attendance. Intra-articular steroid treatment options include hydrocortisone acetate, methylprednisolone acetate, triamcinolone hexacetonide and triamcinolone acetonide. The cost of such treatments will depend on weight of the child and the number of joints affects and range from £0.89 for a 1mL ampule containing 10mg drug to £8.96 for 3mL vial containing 120mg drug[34].

Without knowing which currency code and description was used, it is difficult to determine which cost is most appropriate for treating disease flares and AbbVie would therefore request further information on this point, however, it appears that it may have been underestimated considerably, thereby favouring the methotrexate cohort.

1.5 Limitations of the adjusted indirect comparison

AbbVie agrees with the Assessment Report regarding the nature of the adjusted indirect comparison – it should only be considered an exploratory analysis, rather than being definitive due to the limitations outlined on pages 68-69. These points are similar to those made in AbbVie's submission, but we would like to emphasise that the results should be considered with caution.

Additionally, two points not fully explored in the Assessment Report relate to the definition of disease flare and "placebo response". These points are discussed below.

1.5.1 Definition of disease flare

As noted in the Assessment Report, the definitions of disease flare were broadly consistent between the studies, but some studies had additional criteria such as global assessments and number of active joints. This is particularly relevant to adalimumab as the definition used in, for example, the etanercept trial was less stringent.

Thus conducting an indirect comparison for disease risks comparing 'apples and pears', because the definitions of disease flare differed between trials. Incorporating the results from the indirect comparison in the model would therefore not be reliable and to overcome the bias this approach introduces, AbbVie suggest that an average relative risk (RR) is derived for the biologics in the base case, with ICERs reported in sensitivity analysis for the best and worst case risk of flare based on the lowest and highest flare rates– this would not be unreasonable as the report states there is no evidence of a difference in efficacy and discontinuation rates between biologics (p121) and the confidence intervals for each treatment are wide with no statistically significant difference between the treatments. This suggests that the biologics under review appear to be similar in terms of disease flare.

This approach would also negate the issue with calibration of the "placebo arm" as the reference for relative effectiveness (see below).

1.5.2 'Placebo' arm response.

As stated in the AbbVie submission, calibration of the 'placebo' arms to establish a reference arm for the calculations of relative effectiveness is difficult as the 'placebo' arms are not true placebo responses. A key reason for this which is not mentioned as a limitation in the report is because patients within the different trials may or may not have had the option to take methotrexate. Indeed, as stated on p40 of the report, the majority of patients in the abatacept, adalimumab and tocilizumab trials received methotrexate in addition to a placebo, whereas in the etanercept trial none received methotrexate in the placebo arm. Furthermore, the proportion of patients receiving methotrexate in addition to the biologic ranged from 74%-100%.

This means that it is highly plausible that any differences in efficacy between biologic agents generated from the adjusted indirect comparison do not reflect actual differences between treatments, but instead could be due to, amongst others, the inclusion of methotrexate in the biologic and 'placebo' arm. The report also states that there was clinical heterogeneity between the trials and that there was an unusual high rate of flares in the placebo arm in the etanercept trial. For these reasons any indirect comparison between biologics is misleading, particularly so against etanercept – see Table 26, p70 Table 28, p71 as examples where the wrong conclusions could be drawn.

AbbVie suggests the approach of using an average RR would be more appropriate.

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Section 2. Points of clarification and amendment in the Assessment Report

There are a few areas within the report that AbbVie would like further clarification on or where we suggest amendments, and we present these below.

Inconsistency in referring to polyarthritis – Scientific Summary and Section 1

There is inconsistency within the Assessment Report in referring to polyarthritis. To reiterate, the term 'polyarthritis' in JIA can refer to either the ILAR subtype of JIA at diagnosis for classification purposes (i.e. referring to the ONSET of JIA), or the number of joints affected at any specific time point (polyarticular COURSE JIA). For example, a patient may be diagnosed as having psoriatic arthritis according to the ILAR classification at diagnosis, but may go on to have ≥5 active joints two years later – which means they will also have polyarticular course JIA.

For example on pages 10 and 22, the report states that 'the term polyarthritis also applies to patients who at a particular point in time six months or more after the onset of disease (JIA of any onset type) have five or more active joints'. However, the timepoint is irrelevant to the definition of polyarticular COURSE disease: irrespective of the ILAR classification of the disease at ONSET, if there are 5 or more swollen joints at ***any*** time, the disease is considered to have a polyarticular COURSE.

The report is correct on pages 10 and 22 in stating that 'the concept of polyarticular course JIA has been used for clinical trials and can typically include RF positive and RF negative polyarthritis, extended oligoarthritis, ERA, PA and undifferentiated arthritis. Systemic JIA may also be included in the definition of polyarticular course JIA'. However, technically, the qualifying statement for systemic JIA 'providing there have been no active systemic symptoms during the previous six months' is not quite correct: systemic onset JIA could still be polyarticular COURSE, even in the presence of systemic symptoms. However in the case of active systemic symptoms, anti-TNFs and abatacept would not be used clinically as first line biologic treatments, and therefore AbbVie agrees systemic onset JIA with active systemic symptoms is outwith the scope of this NICE appraisal. This is referenced correctly in Table 1, page 21.

Therefore, suggested amendments include for example:

- Page 10, and throughout where relevant would be: 'this appraisal includes all sub-types of ***polyarticular course*** JIA with the exception of systemic JIA ***with active systemic features*** or persistent oligoarticular JIA'.
    - Table 5 on page 32: should be updated to reflect the above.
    - Page 142: The following statement should be updated to reflect the above: 'The modelled patient population is therefore people with JIA, with the results of particular relevance to those with polyarticular course JIA (extended oligoarthritis, and RF + ve and RF – ve polyarthritis).'
- Undifferentiated arthritis should be added to the following:
    - On page 36: undifferentiated arthritis should be added to the following statement: 'similarly, patients with ERA and PA that has a polyarticular course will also be included'.

Undifferentiated arthritis - Section 1

Table 1 on p20 of the report describes the various JIA classifications and indicates whether this is included within the NICE appraisal scope. Unlike the other types of JIA, it is not indicated in the table whether undifferentiated arthritis is included in the scope or not.

Data from adalimumab ongoing trial 1 which are unclear to the Assessment Group - Section 4.3

AbbVie wishes to inform the Assessment Group that after the Assessment Report was produced this study has been published in full as *Burgos-Vargas R et al. A randomized, double-blind, placebo-controlled, multicenter study of adalimumab in pediatric patients with enthesitis-related arthritis. Arthritis Care Res (Hoboken). 2015 Jul 20. doi: 10.1002/acr.22657*.

On p81 of the report it is stated, with reference to the clinical study NCT01166282 that "It is unclear if patients also received methotrexate". Information in this paper confirms that concomitant use of stable doses of a corticosteroid, NSAID, or DMARD was allowed. Additionally, the report also states that **"**is unclear if baseline characteristics between the treatment groups were balanced." In Table 1 from the published paper it can be seen that there were no statsitically significant differences in baseline charactieristics between the 2 arms.

Within-scope biologics with recommendations for the use of uveitis - Scientific Summary and Section 4.4.2

AbbVie considers that the statements in the Scientific Summary, p13 and Section 4.4.2 that adalimumab appears more effective than etanercept may be misinterpreted as etanercept being a treatment option, when etanercept is not recommended for this group of patients and the Assessment Group did not consider potentially modelling etanercept for JIA-U. This is confounded by a statement on p154 which erroneously states that etanercept is included in the draft NHS clinical commissioning policy on the use of anti-TNF alpha agents. (See Section 3 for more details).

As noted in the Assessment Report, a draft NHS clinical commissioning policy on the use of anti-TNF alpha agents in paediatric patients with severe refractory uveitis states that etanercept <u>is not recommended</u> for use in this patient group. The report goes on to state that potential modelling of the clinical- and cost-effectiveness in JIA-U would only apply to adalimumab as this is the <u>only one of the four biologics</u> within the scope of the appraisal recommended for treating this sub-group (Section 5.7.3, p143).

Additionally, the etanercept Summary of Product Characteristics (SPC) states in Section 4.4. Special Warnings and Precautions for use that *"There have been reports of IBD and uveitis in JIA patients being treated with Enbrel (see section 4.8)."* Section 4.8 Undesirable effects, states *"There have been reports of inflammatory bowel disease and uveitis in JIA patients being treated with Enbrel from post-marketing sources, including a very small number of cases indicating a positive rechallenge (see section 4.4)".* Uveitis is also listed as an uncommon side effect in Section 4.8.

More reasonable statements would be that adalimumab appears to be effective in this group of patients, without comparing it against etanercept – as is stated in Section 7.1.2 (p152). As such AbbVie requests that the statements in the Scientific Summary and 4.4.2 be amended to this effect

to avoid the interpretation that etanercept could be used in patients with JIA-U. Alternatively, addition of the text from e.g. the draft NHS clinical commissioning policy and Scottish Uveitis National Managed Clinical Network Treatment Guidelines would provide further clarity on the use of biologics in JIA-U.

STRIVE registry adverse event data – Section 5.6.1

The Assessment Report uses the STRIVE registry for the methotrexate discontinuation rate for adverse events and quotes that 2.3% of patients per year discontinued in this group. Although this is referenced to the AbbVie submission, it is not clear where within the submission this was obtained as the five-year discontinuation rate due to adverse events was 6.6%, as reported in the submission and referenced to Brunner et al[35].

Various sections – Cross referencing on p40, p41, p45, p46, p211

It appears the original text may have become corrupted and replaced with the text **Error! Reference source not found**. It would be helpful to the reader to view the original text.

Various sections – Table numbering on p107, p127, p136

It appears the table numbers have been replaced by the table title. It would be helpful for the reader to have the table number instead of the title.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis (including review of TA35) [ID783]

The economic model enclosed and its contents are confidential and are protected by intellectual property rights, which are owned by Southampton Health Technology Assessment Centre. It has been sent to you for information only. It cannot be used for any other purpose than to inform your understanding of the appraisal. Accordingly, neither the model nor its contents should be divulged to anyone other than those individuals within your organisation who need to see to them to enable you to prepare your response. Those to whom you do show the documents must be advised they are bound by the terms of the Confidentiality Agreement Form that has already been signed and returned to the Institute by your organisation.

You may not make copies of the file and you must delete the file from your records when the appraisal process, and any possible appeal, are complete. If asked, you must confirm to us in writing that you have done so. You may not publish it in whole or part, or use it to inform the development of other economic models.

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

July 2015

Issue 1 Functionality of drop-down menu for sensitivity analyses (model 1 and 2)

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
On the Parameters tab, cell D1 has a note regarding the drop down options that will allow the user to change the parameters from deterministic to probabilistic or sensitivity analysis. However, the drop down menu does not appear populated and it is not possible to overwrite the text in cell D1. This in turn does not allow the live values in column B to be changed and the user therefore can't easily verify the results for the deterministic and probabilistic sensitivity analyses.	Correcting the drop-down menu so that the user can trigger the values	Improved use-ability of the model

Issue 2 Half-cycle correction (model 1 and 2)

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
No half-cycle correction was applied in the model	Half-cycle correction should be applied e.g. by halving the total costs and QALYs in the first and last cycle	The changes to the ICERs are expected to be minor and in the range of £400-£600 lower depending on the biologic drug in first line use. The model was not re-run for the 2nd line biologic model or sensitivity analyses

Issue 3 Formulas for AE discontinuation in Markov trace tabs (models 1 and 2)

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Adalimumab Tab Cell G5 contains the formula: (1-$E$4)*F5*Efficacy!$D$22 (with the remainder of the column using the same value highlighted in yellow) This is repeated in the methotrexate, etanercept, tocilizumab and abatacept tabs	The formula should be: (1-E5)*F5*Efficacy!$D$22 with subsequent cells in the column referring to the corresponding value in column E	It has no noticeable effect on the ICER.

Issue 4 Formulas for disease flare in methotrexate Markov trace tab (model 1 and 2)

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
MTX Tab Cell AB4 contains the formula: =DF_EtN*W4 (with the remainder of the column using the formula =DF_Pbo*W5)	The formula should be: =DF_Pbo*W5	The deterministic ICERs for the biologics are lower in Model 1: Adalimumab: £38,023 Etanercept: £32,435 Tocilizumab: £38,557 The model was not re-run for the 2nd line biologic model or for sensitivity analyses

(please cut and paste further tables as necessary)