Roche response to assessment report on JIA

Thank you for giving us the opportunity to comment on the Assessment Report (AR) for the Juvenile Idiopathic Arthritis (JIA) multiple technology appraisal. We are pleased that the AR has recognised the important role that biologic disease-modifying anti-rheumatic drugs (bDMARDs) play in the treatment of children with JIA.

We agree with several of the methods and assumptions of the AR. However, our review identified a number of crucial issues which concerned us about the balance and diligence regarding the synthesis of the clinical evidence, and consequently the analysis results; both regarding the adjusted indirect treatment comparison (ITC) and the economic model.

In particular, we appreciate that the AR recognises a number of issues and limitations of the existing evidence base that render the adjusted ITC exploratory. However, the AR fails to recognise a fundamental limitation in the use of disease flare as an efficacy parameter when comparing different treatments; the incidence of disease flare is only one dimension of treatment efficacy. The occurrence of disease flare does not provide enough information on the severity and its impact on the patient's condition, both crucial elements for a treatment comparison. It follows that by using disease flare in an ITC, the efficacy of treatments that achieve sustained levels of disease improvement will be underestimated. We provide more details below (please see issue 1).

The simplistic assumption of levelling the impact of all disease flares is also problematic in the calculation of health-related quality of life (HRQoL) for patients. In the SHTAC model the disease flare disutility is assumed fixed. However, the impact of disease flare on patients' utility can vary depending on the worsening of the patients' condition (≥30%) or the baseline HRQoL of patients (please see issue 4). If such an analysis is not performed, the model suffers from significant structural uncertainty and other ways of conceptualising the model structure should be explored.

An alternative method of comparing across the bDMARDs (both in the ITC and economic model) is possible by using ACRpedi response. This method too has limitations as, unfortunately, there are differences in the way missing information is imputed across all trials (please see issue 3). Nevertheless, it allows a more accurate representation of treatment efficacy and if combined with other parameters (e.g. discontinuation) it provides a more rounded assessment of the impact of each treatment on the patients' condition. We provide a re-analysis based on ACRpedi below (please see issue 1).

We identified a number of additional computational errors (issues 6-11) that are less crucial compared to the issues identified above. Nevertheless, they illustrate lack of proper audit and shortcomings in the accuracy of the SHTAC model methods and results.

Issue 1 Use of disease flare as the main efficacy parameter of bDMARDs in the NMA and the model

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Although the primary endpoint of the clinical trials is disease flare, a comparison of treatments based on this outcome is clinically less meaningful than ACRpedi response. With ACRpedi response we can determine the categorical improvement of patients with one treatment vs. another; within a specified range 30-50%, 50-70%, 70-90%, 90%+. This is useful information as the relative improvement across treatments may differ substantially; for example, there could be treatments that barely achieve ACRpedi30 and treatments that achieve much higher levels of response. The occurrence of disease flare does not provide any information on the severity of the flare and therefore it is less useful when comparing across different treatments. For example, if a patient experiences a 90% worsening, this has the same weight as if they experienced a 30% worsening. The two types of disease flare are not clinically the same, however, in the ITC and model they are assumed to be. This leads to a significant underestimation of the efficacy of treatments that achieve and sustain high levels of disease improvement.	The efficacy of the bDMARDs in the model should change to reflect the evidence on categorical improvement of treatment (ACRpedi response levels).	We cannot verify the impact of this change on the SHTAC model. However we re-ran the analysis with the Roche model after correcting the errors identified in our model by the AG. We provide details on some of the methods and results below.

Methods of the re-analysis:

We removed the subsequent bDMARD treatment lines and assumed a comparison of each bDMARD against control (methotrexate or placebo) as in the SHTAC model. We used the evidence on tocilizumab vs adalimumab (Brunner 2012, Lovell 2008 – see issue 3) for the ACRpedi response data (CS). We corrected the calculations on QALYs and used the mortality risk suggested by the AG (0.03%). We used the response-dependent discontinuation risks (CS) in the first 6 months, and thereafter used the same risk as in the SHTAC model: (7+29)/105.

Results were weighted 20/80 for mono/combo population. The revised model is available for audit and appraisal.

Results of the re-analysis:

The tables below present the results in the comparison against methotrexate/placebo, etanercept and adalimumab, in the same format as presented in the AR (pairwise comparisons vs. control).

Cost-effectiveness of 1st bDMARDs without PAS

	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER £/QALY
Methotrexate or Placebo	£59,333	9.83			
Adalimumab	£109,421	11.39	£50,088	1.57	£31,993
Etanercept	£106,469	11.39	£47,137	1.56	£30,182
Tocilizumab	£108,950	11.39	£49,617	1.56	£31,709

Cost-effectiveness of 1st bDMARDs with confidential PAS

	Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER £/QALY
Methotrexate or Placebo	£59,333	9.83			
Adalimumab	£109,421	11.39	£50,088	1.57	£31,993
Etanercept	£106,469	11.39	£47,137	1.56	£30,182
Tocilizumab	[redacted]	11.39	[redacted]	1.56	[redacted]

Discussion –comparison with SHTAC results:

The total QALYs in the Roche model are similar to the ones generated with the SHTAC model. The total costs are lower. This is probably due to the differences in the resource use cost used (Prince 2011 has lower costs than Thornton 2008).

The Roche model includes AEs for the bDMARDs (infection -4% per year) but does not differentiate discontinuation between AEs and inefficacy in the first cycle. Nevertheless, the Roche model uses evidence from a cohort study (ABC), which is likely to combine the discontinuation due to either cause –as done in the SHTAC model. Note that the average discontinuation risk in the first 6 months is higher in the Roche model than in the SHTAC.

Issue 2 ITC on disease flare and impact of lead-in phase

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The ITC results on disease flare are biased and the AR does not cover the full extent of the heterogeneity and dissimilarity of the evidence in the randomised phase of the withdrawal control trials (WCTs). The maintenance of the treatment effect from the lead-in phase was not considered. Application of the typical ITC methods on the randomised phase will favour agents with short-lived treatment effect compared with treatments with a long-lasting effect; the difference between active and control arms is exaggerated in a “shorter”-effect agent. For example, the shorter half-life of etanercept is likely to overestimate the difference between etanercept and placebo in the randomised phase, leading to results that favour etanercept against the other comparators.	N/A	N/A

Issue 3 ITC on ACRpedi outcomes

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The ITC on ACRpedi50 and ACRpedi70 response suffers from additional bias related to significant differences in the way the studies handled missing data at the end of the randomised phase. Lovel 2000 and Ruperto 2008 imputed missing values using the last observation carried forward	Given the similarities in terms of the trial design, the lead-in phase duration, the patient population, and the methods of imputation between Lovell 2008 and Bruner 2012 only adalimumab and tocilizumab could be compared via an indirect comparison.	ACRPedi evidence submitted with the Roche CS.

(LOCF) method, with ACRpedi response recorded at the end of the follow-up or carried forward from the time of flare. Lovell 2008 and Bruner 2012 used a non-responder imputation (NRI) method for missing data. The authors stated that patients who experienced a flare during the double-blind phase were classified as non-responders regardless of the actual ACRpedi responses. This introduces a significant difference in the measurement of the outcomes considered. In essence, in tables 27 and 28 the AR presents results of non-comparable outcomes.		

Issue 4 Disease flare disutility

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The disease flare disutility is assumed to be fixed. However, the impact of disease flare on patients' utility can vary depending on the worsening of the patient condition (≥30%) or the baseline HRQoL of patients. The analysis of the impact of disease flare on patients' HRQoL is very simplistic as it does not take into account all important contributing factors. The current approach does a disservice to treatments with sustained high response levels, when patients experience flares of 30% compared to treatments/cases where more severe flares occur.	See issue 1 on proposed changes to the model.	See issue 1

Issue 5 First model cycle treatment discontinuation

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The model uses evidence from the lead-in phase of the studies for the discontinuation risk in the first cycle. This implies a naïve comparison of study results and ignores several differences that could influence discontinuation due to AEs or inefficacy; such as the duration of the lead-in phase, background treatments (mono/combo), differences in the trial populations etc.	The base-case analysis should use a different method of estimating discontinuation in the first (and subsequent) cycle. It is possible to assume different treatment discontinuation risks for each treatment, based on the level of response (evidence submitted in Roche CS).	See issue 1

Issue 6 2nd line model; abatacept total cost

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The cost per cycle for abatacept is incorrect.	The model should estimate 3.25 doses per cycle	The ICER for abatacept increases by about £2,000 per QALY gained.

Issue 7 Incorrect calculations of probabilities for subsequent cycles

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The calculation of the discontinuation probabilities for subsequent cycles (P_{4y}-P_{1st_cycle})/15 is incorrect and underestimates the cumulative discontinuation probability at 4 years. Note that a similar error occurs in the calculations of the probability of death (mortality/4) and remission. However, it is	The calculations neglect the fact that probabilities cannot be added or subtracted like rates.	The ICER is not expected to change substantially.

unclear why the probability of remission is divided by 3, as this is not covered in the AR.		

Issue 8 Half-cycle correction

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Half-cycle correction is not implemented in the model	Apply half-cycle correction to costs and QALYs	The ICER is not expected to change substantially. The total costs and QALYs will change, but not the incremental values.

Issue 9 MTX disease flare risk

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Incorrect risk of disease flare is used in the first cycle in the MTX model (MTX tab, cell AB4)	Link the formula to DF_Pbo	The ICER is not expected to change substantially.

Issue 10 MTX remission cost

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The MTX remission cost calculation (MTX cell AS4:AS284) is incorrectly referring to a cell with an etanercept input (Drug costs cell F36).	The MTX remission cost formula should be linked to the placebo input (Drug costs cell C36).	This affects only the sensitivity analysis with remission. The ICER is not expected to change dramatically.

Issue 11 Typo in the table with the cost-effectiveness results

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Table 58, p. 132, contains a typo in the results of the standard of care strategy (methotrexate).	N/A	N/A