NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Vedolizumab for treating moderate to severe active Crohn's disease after prior therapy

Dear Ross,

The Evidence Review Group, **School of Health & Related Research Sheffield (ScHARR)** and the technical team at NICE have now had an opportunity to take a look at the submission received on the **22nd August 2014** by Takeda. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **2nd October 2014.** Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted], Technical Lead [redacted]. Any procedural questions should be addressed to [redacted], Project Manager [redacted] in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Context

A1. **Priority:** The company refers in several places to the CSR of the GEMINI II and III studies. Please provide the CSR for these studies.

A2. In GEMINI II and III a proportion of patients did not receive prior TNF-alpha inhibitors. Please clarify whether some patients were not exposed to TNF-alpha inhibitors because they were intolerant or contraindicated? Please provide the proportion of patients in the TNF-alpha inhibitor naive subgroup that were intolerant to TNF-alpha inhibitors or contraindicated.

A3. The Company submission states (p.36-37) that vedolizumab is contraindicated in patients with active tuberculosis (TB), and that screening for TB should be undertaken. It also states that patients with active, severe infections should not receive vedolizumab until the infection has been controlled, and that physicians should consider stopping treatment in patients who develop a severe infection while on chronic treatment with vedolizumab. For the TNF-alpha inhibitors currently in use in the UK, screening must be undertaken for HIV, Hepatitis B and C and for heart conditions, alongside a consideration of people who are eligible to receive an influenza vaccination. Please clarify whether screening is also required for people taking vedolizumab for viruses such as HIV, Hepatitis B and C and cardiac conditions. If there is no requirement please provide an explanation of why this is the case.

A4. Please clarify the sentence: 'As a result of the lack of data, the vedolizumab product information contains details on infections, neurological symptoms and infusion relation reactions' (p. 37). Please provide the type and number of possible infusion-related reactions experienced with vedolizumab.

A5. Please clarify whether infusions with vedolizumab will be administered in hospital. What are the implications of hospital based administration of vedolizumab compared with the currently used TNF-alpha inhibitors, which can be administered in the home? (p.37) For TNF-alpha inhibitors administered at the hospital, please clarify whether the

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administration of vedolizumab at hospital would be different to the administration for TNF-alpha inhibitors.

A6. The wording of the indication in NICE's scope suggests vedolizumab could be placed anywhere in the treatment pathway after a conventional therapy has been tried. This presumably could include using vedolizumab after failure of corticosteroid. Please confirm your understanding of the position of vedolizumab in the pathway, providing further explanation of figure 3.5.1 page 49.

Conduct of the systematic review

Literature searching

A7. It appears that the company used published search filters. Please could references be provided for the search filters employed in the various search strategies (clinical and economic)?

A8. The search strategy for the economic element of the report appears to be missing. Please provide this search strategy.

Inclusion / exclusion criteria

A9. Page 68 – Table 6.2.1.2 of the company's submission states that prospective studies with more than 1 treatment arm were included at level 2 screening. However, none have been included in the NMA. Please clarify whether none were found, or whether the inclusion criteria were incorrect.

Data synthesis, analysis

Comparability of usual care as defined in Gemini II and III with usual care in the UK.

A10. **Priority**: Please provide data on the number and type of infusion-related reactions for vedolizumab in GEMINI II and III.

A11. Pages 75 to 83 state patients had to have failed on immunomodulators, TNF-alpha inhibitors or corticosteroids to be eligible for enrolment in GEMINI II and III. In the UK, patients would have to have failed on corticosteroids before being eligible for immunomodulators or TNF-alpha inhibitors.

- Had all people in the GEMINI II and III trials experienced a previous failure of corticosteroid treatment?

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- Please clarify how any differences in the prior management protocol of patients recruited to these trials will impact on:
  - the spectrum of patients recruited
  - generalisability of findings to the UK
  - estimates of efficacy.

A12. The description of the top down approach "traditional treatment strategy" described and illustrated in figure 2.6.2 – page 52 suggests the "step up" approach places 5-ASA and antibiotics as the first treatments in the treatment pathway. NICE clinical guideline152 (CG152) suggests people would take corticosteroids first, then 5-ASA where these fail/are contraindicated/ not tolerated. Please provide evidence to support your statement that "the traditional strategy is the norm in the UK", as this does not appear to be the case.

A13. Page 75 - Please clarify what the treatment regimen was for patients in GEMINI II and III placebo arms. Was the treatment pathway the same as CG152? With reference to figure 2.6.2, in what circumstances was 5-ASA used?

Patient characteristics

A14. **Priority**: Table 6.3.4.1 – patient characteristics (Page 84 to 86). For both trials please clarify to what extent the patient spectrum in each trial differs from the UK patient spectrum who would be eligible for treatment with vedolizumab. Please ensure your response makes reference to the following points:

GEMINI II:

- Please clarify how the 35% of patients who were receiving neither corticosteroids nor immunosuppressants were being treated. Were they being treated in accordance with CG152?
- Please provide % on TNF-alpha inhibitors at recruitment
- There appears to be differences in baseline characteristics for faecal calprotectin and prior surgery. Were these differences likely to affect estimates of efficacy? Were any corrections to results attempted for these differences? If not, why not?

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GEMINI III:

- Please provide % receiving neither corticosteroids nor immunosuppressants and clarify whether they were being treated in accordance with CG152.
- Please provide % on TNF-alpha inhibitors at recruitment
- There appears to be differences in baseline characteristics for history of fistulising disease, prior surgery in TNF-alpha-inhibitor-naïve groups (placebo vs intervention arm), prior immunosuppressive exposure (TNF-alpha-inhibitor-failure population, placebo vs intervention arm); 1 prior TNF-alpha inhibitor failure (placebo vs intervention arm in TNF-alpha-inhibitor-failure groups). Were these differences likely to affect estimates of efficacy? Were any corrections to results attempted for these differences? If not, why not?

A15. Please could details be provided of the number of participants from each of the centres, and their ethnicity? Is the overall patient population generalisable to the UK population?

A16. p.95 The results for the predefined subgroup analyses of faecal calprotectin <500 mcg/g and>500 mcg/g are not presented. Please provide the results of these analyses.

A17. Was assessment of treatment by strata interaction undertaken? If so, please provide the results.

Recruitment

A18. **Priority**: On page 62 the statement of the decision problem states that in the final scope issued by NICE the population of interest is 'Adults with moderately to severely active Crohn's disease.....' and that 'The patient population considered within this appraisal is in line with the final scope population.' It is stated on page 39 that a CDAI score of >450 indicates severe disease, and the trial inclusion criteria for population gives a cut-off of 450 on CDAI (p. 83), which according to the submission, indicates moderate disease. (Although, Gemini II analysed data on patients scoring between 220-450, and 220-400 for Gemini III). Therefore, although the submission claims to present evidence on moderate to severe Crohn's disease on this measure, it appears patients with severe disease have been excluded. Please clarify:

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- the definition of severe disease
- whether people with severe disease were included in the GEMINI trials
- whether there was some other factor on which severity was being measured – e.g. faecal calprotectin?

A19. Table 6.3.2.1 – GEMINI II - what is the rationale for limiting patients with previous exposure to TNF-alpha inhibitors to 50%? Please clarify how this will impact on generalisability of findings to the UK, and estimates of efficacy?

A20. Page 83 states that the eligibility criteria of GEMINI II and III were identical. Please clarify if both trials limited TNF-alpha-inhibitor-exposed patients to 50%? Were there any other differences in how patients were recruited for the two trials?

A21. Why were patients with intestinal strictures excluded from the study population (page 83)? How will this impact on generalisability of findings to the UK population?

A22. Please provide a table of baseline characteristics for the TNF alpha-inhibitor-naïve population in GEMINI II (induction phase and maintenance phase) and GEMINI III for both the placebo and vedolizumab arm.

A23. Please provide the number of patients at baseline with CDAI<150, CDAI 150≤220 and CDAI over 220 from the GEMINI III study, by treatment arm.

A24. Please provide the number of patients at baseline with CDAI<150, CDAI 150≤220 and CDAI over 220 from the GEMINI II study, by treatment arm, at the beginning of the trial (induction phase), and after randomisation to the maintenance phase (2nd randomisation).

Dosing schedule in GEMINI II and III

A25. **Priority**: Table 6.2.4.1 states that vedolizumab in GEMINI II was administered at weeks 0, 2. However, Table 6.3.2.1 states that vedolizumab was administered at weeks 0 and 6. Please clarify which is correct.

Furthermore, in Table 6.3.2.1, the dosing schedule for GEMINI III is at weeks 0, 2 and 6. Please clarify the dosing schedule in GEMINI II and GEMINI III. Please explain the differences in dosing schedule between the GEMINI trials, if any. If there are

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differences in schedule/dosage, please clarify which trial is relevant to this assessment (has a dosing schedule of vedolizumab in line with licensing).

A26. In GEMINI III, please confirm whether 2 or 3 doses were received by the assessment at week 6 when the outcomes were measured.

Patient flow

A27. How many patients crossed over treatment arms in each GEMINI trial? Please present the number of patients who crossed over in each treatment arm separately.

A28. Were any patients lost to follow up (as opposed to withdrawing from the trial) and if so, how was missing data handled?

A29. What were the reasons for discontinuation (figure 6.3.8.1 GEMINI II & 6.3.8.2 GEMINI III)

Study quality

A30. Please clarify how blinding was achieved in GEMINI III (the equivalent information to that given for GEMINI II in table 6.3.2.1).

Maintenance phase

A31. **Priority**: Please provide baseline patient characteristic data for patients entering the maintenance phase of GEMINI II, for both the placebo and intervention arms.

A32. Please clarify the definition of “clinical response” that was used as eligibility criteria for entry into the maintenance phase of GEMINI II.

Outcomes

A33. **Priority**: Please provide a rationale for the choice of 6 weeks for the primary outcome (remission/response) in GEMINI II. Why were outcomes measured at 10 weeks in GEMINI III yet 6 weeks in GEMINI II (page 74)? The ERG’s clinical experts suggest 12-14 weeks is a more usual assessment point, please explain why outcomes were not reported at these time points.

A34. **Priority**: p.80; 88: Primary outcomes are listed as remission <150 on CDAI and enhanced clinical response >100 decrease in CDAI at 6 weeks – however, the

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response outcome reported later (p109) is decrease in CDAI >70 – Please provide clarification on this.

Results of the trials

A35. Table 6.5.3.6 has no p values. Please clarify why, or provide the values.

NMA

A36. **Priority**: Page148 – data for natalizumab is reported in the summary of the MTC results. Please clarify whether this is a typo, or whether natalizumab had not been removed from the network. In either case, please provide the corrected text relating to the network without natalizumab.

A37. **Priority**: Please clarify whether it is possible to classify patients into one of three mutually exclusive categories: Remission (CDAI ≤ 150), Enhanced response (CDAI > 150 and reduction CDAI ≥ 100), Response (CDAI > 150 and reduction 100 > CDAI ≥ 70), No response (CDAI > 150 and reduction CDAI<70). If so, please provide results from the MTC.

A38. **Priority**: Please complete the reviewer's checklist as presented in Ades et al; Evidence Synthesis for Decision Making: A Reviewer's Checklist. Medical Decision Making 2013; 33: 679-691

A39. **Priority**: Please provide information on the prior distributions that were used in each Bayesian network meta-analysis.

A40. **Priority**: Please explain how adjustments for multi-arm trials were incorporated into the Bayesian network meta-analyses when using the BUGS code presented in Figure 10.14.2.

A41. **Priority**: Please provide the initial values for the Markov chain Monte Carlo (MCMC) simulations and provide evidence that the Markov chains converged within a burn-in of 20,000 iterations.

A42. **Priority**: Please confirm the number of MCMC iterations used to estimate parameters and provide information on the MC error for each parameter.

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A43. **Priority**: Please provide the arm-specific and total residual deviances and compare them with the number of data points included in each analysis.

A44. **Priority**: Please provide estimates of the between-study standard deviations and associated 95% credible intervals for each Bayesian network meta-analysis.

A45. **Priority**: Please provide estimates of the odds ratios and 95% credible intervals for the effect of each treatment in a new study (i.e. the predictive distributions).

A46. **Priority**: Please clarify which analyses involved closed loops of evidence other than those formed by multi-arm trials.

A47. **Priority**: Please provide estimates of the between study standard deviations on the log odds scale when combining the placebo response rates across studies.

A48. Please describe how meta-regression was performed, including the specific statistical models used, what assumptions were made about the relationship between treatment effect and treatment effect modifier for each treatment, and the prior distribution(s) used for the regression parameter(s).

A49. Study selection criteria do not appear to list “moderate to severe” Crohn’s as an inclusion criteria. Please clarify whether patient disease severity was used as an inclusion criterion. It appears from the Takeda data on file that all studies were in moderate to severe Crohn’s disease patients. Please clarify why one study has a much lower mean CDAI score than the others.

A50. Please confirm that the results presented in Table 6.7.6.1 of the STA report are from the same statistical model as for the results presented in Table 21 of the Takeda Data on File 2014 document.

A51. Please clarify why the complimentary log-log link function did not allow for a random treatment effect.

A52. Please clarify whether the inconsistency checks are a comparison between direct and indirect evidence in closed loops of something else.

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A53. Why has the network meta-analysis of adverse events used the outcome "discontinuation due to AE's"? Was a network possible for AE and SAE, either as rates per person year (or week) or as number of patients experiencing an event? If so, please provide the results of these NMA.

Section B: Clarification on cost-effectiveness data

Cost-effectiveness results

B1. **Priority:** In the incremental analysis for the TNF-alpha-inhibitor-naïve population, please clarify why results from the head-to-head trials GEMINI II and III were used to estimate the percentage of patients in remission and who had a response for the vedolizumab and conventional therapies arms rather than using the results of the MTC as for other treatments (infliximab and adalimumab)?

B2. **Priority:** The company reports results for patients with moderate and severe disease at baseline separately. It unclear how these analyses were conducted and the data and assumptions that were used to derive these analyses because the company's model does not appear to include the option to conduct an analysis for these subgroups of patients. Please provide details on how these analyses were conducted, the data used (utility values, transition matrices, response rates, remission rates, costs) and the assumptions made. Furthermore please clarify how these subgroups were defined, for example on CDAI score?

Effectiveness data

B3. **Priority:** Please clarify why the CODA (Convergence Diagnostic and Output Analysis) samples from the network meta-analysis were not used as inputs to the economic model. Please provide the CODA samples.

B4. **Priority:** In page 219 (Table 7.3.1.2) please clarify the source of data and calculation for the probability of response/remission with infliximab. The company states that the averages of the week-2 and week-10 assessments from the ACT-1 trial were used to estimate a week-6 response for Infliximab. Please provide the data at week 2 and week 10 from this study. Please clarify whether data at at week 6 is available?

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B5. **Priority:** Please clarify how the baseline placebo response and remission rates were calculated.

Model structure

B6. **Priority:** The structure of the model is based on a model previously published by Bodger et al (2009). The company implies that the model structure used by Bodger et al (2009) was recommended by the Decision Support Unit (DSU) but where a reference to this could not be found in the DSU report. Please clarify the section of the DSU report which recommends this particular model structure.

B7. **Priority:** No reference is made in the company submission to the model structure used in NICE CG152. Please clarify whether such a model structure was considered and the rationale for choosing the model structure from Bodger et al (2009) over the model structure used in NICE CG152?

B8. **Priority:** A stopping rule is applied at 1 year for all biologics. Please clarify how this reflects clinical practice. Please clarify why no analyses were conducted assuming a no stopping rule?

B9. **Priority:** Please clarify why the same induction period was assumed for the biologics rather than assuming a different induction period for each biologic? Please provide the list of any additional assumptions that would be required if assuming a different induction period for each biologic.

B10. **Priority:** Please clarify why 'response70' is used in the base case to define patients who would be deemed to have responded to treatment, rather than other indicators such as remission?

B11. **Priority:** Please provide a description of the outcomes in Cell I72 and H72 (expected results) in the 'Markov Vedo sheet' in the economic model.

B12. It is assumed that responders can either be in remission or have moderate/severe disease. Please clarify why a responder cannot be in the mild health state (CDAI: 150-220)?

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B13. Please clarify whether relapse following biologic cessation has been included in the economic model?

B14. Please explain why the proportion of responders in moderate/severe is assumed to be the same for vedolizumab and conventional therapy when trial data are available. Please provide data from the trial.

B15. Please clarify why a 10 year time horizon was selected rather than a lifetime horizon?

B16. Please clarify why response was used for patients on conventional therapy rather than deriving a general transition matrix from the beginning of treatment?

B17. It is assumed that the proportion of responders that are in the moderate/severe health states are the same for all biologics. Please clarify whether this assumption is supported by clinical data.

B18. Currently the remission rate for adalimumab was set equal to the response rate. Please clarify why this assumption was preferred to setting the response rate equal to the remission rate?

B19. It is assumed that following failure of biologics, a proportion of patients would respond to conventional therapy based on the response rate for patients initially treated with conventional therapy. Please clarify whether this assumption (i.e. response rate in usual care in TNF-alpha inhibitor-naïve and TNF-alpha inhibitor- failure are similar) is supported by clinical data?

Model calibration/prediction

B20. **Priority:** Transition matrices are calibrated using solver (Excel). Please clarify why different starting values are used for the conventional therapy and vedolizumab arms? Please clarify how the starting values were selected?

B21. **Priority:** Limited information is provided in the company submission on the process of the calibration exercise and the rationale and selection of the different constraints. The company refers to Appendix 15 (section 10.15) of the submission for further details but the relevant appendix describing the calibration process and assumptions used was

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not found. Please provide details on the calibration process and a list and rationale for the assumptions and constraints used.

B22. **Priority:** The economic model predicts that a greater number of patients would die in the conventional arm compared with the vedolizumab arm at one year. Please clarify how the model prediction compares with the trial data at one year.

Inconsistencies

B23. **Priority:** In the economic model, patients stop treatment with biologics at cycle 6 (week 46). Please clarify why the stopping rule is applied at cycle 6 (week 46) rather than cycle 7 (week 54)?

B24. **Priority:** Please clarify whether the model is calibrated to outcomes at week 46 or 54?

B25. **Priority:** On page 211, the company states that following surgery patients receive conventional therapy. However, in the economic model, a transition probability is added for patients to remain in the surgery health state, and therefore patients can remain in this health for more than on cycle. Please clarify this inconsistency.

B26. Please clarify the differences in the proportion of patients in remission with infliximab for the TNF-alpha inhibitor-naïve population between the values used in the model (34.50%) and presented in the report (37.0%).

Costing

B27. **Priority:** As stated by company, there are differences between the induction period in the trial and the licensing of biologics. Please clarify whether costs for the induction period (for each biologics) are calculated according to the induction period (schedule) in the trials or the induction period recommended by the licensing.

Please provide clear statements and references for the assumptions and sources used for the induction phase for vedolizumab, adalimumab and infliximab (i.e. trial used or licensing or assumptions)

B28. **Priority:** On page 216 the company states that *'a patient in remission incurs costs of £236.52 per cycle (8 weeks). Within the model, it is assumed that this includes routine monitoring of CD'*. However, on page 305, the cost for the remission health state is

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£110. Please clarify this inconsistency and how the cost for monitoring is included within the economic model

B29. Please clarify why the cost for conventional therapies was derived from a UK audit rather than from the number and type of therapies used in the trial directly. Please provide the proportion from the trial (by treatment arm) and a comparison with data from the UK audit.

B30. Please clarify why it is arbitrarily assumed that 50% of patients treated with biologics receive conventional therapies. Is this assumption supported by the trial data?

B31. Health state costs (except surgery) are taken from Bodger et al (2009). In the PSA and SA, costs are varied from a gamma distribution assuming an arbitrary 20% in tails. Please clarify why the standard deviation/error from Bodger et al (2009) was not used to estimate the uncertainty in this parameter?

B32. The cost of surgery was derived from NHS reference costs and varied from a gamma distribution assuming an arbitrary 20% in tails. Please clarify why the uncertainty was not captured using the range reported in the NHS reference costs?

B33. On page 300 (Table 7.5.1.1), please clarify why NHS Reference Costs 2011/12 (and/or uplifting costs to 2012) were used when more recent years are available (same for BNF)?

B34 In tables 7.2.7.1 and 7.3.6.1 prednisolone has been costed as a metered application (presumably for topical use) whereas prednisolone is used orally for inducing remission (see definition of inadequate response in the Glossary). Please clarify whether it has been assumed that prednisolone is given as rectal foam for the purposes of the model.

Adverse events

B35. Please clarify how the studies used to calculate the rate of AEs were selected. Please clarify whether these were the same studies from which clinical data used for efficacy in the economic model were obatined.

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B36. The rate of AEs is calculated as the number of patients affected divided by the total number of patients. However, the trials included had different follow-up duration. Please amend the calculation to estimate the rate of adverse events per week (to allow comparison between treatments).

B37. On page 224 (Table 7.3.1.7), the calculated probabilities of AEs are assumed to be greater for patients on conventional therapy compared with vedolizumab. Please provide a comparison with results from the GEMINI studies.

B38. On page 223 (Table 7.3.1.6), please clarify that the probability of discontinuation is per year. Furthermore, please clarify how the discontinuation rate in Table 7.3.1.6 relates to the discontinuation rate in the clinical section (section 6.7). Please clarify why the discontinuation rate for infliximab was assumed to be the same as for adalimumab. Please clarify whether an analysis been conducted assuming the same discontinuation rate for all treatments (infliximab, adalimumab, vedolizumab). If so please provide the results of this analysis analysis.

B39. It is assumed that AEs are managed in the hospital setting. Please clarify the rationale for this assumption. Furthermore, please clarify whether AEs were managed at the hospital in the GEMINI II and III trials.

Utility values

B40. Utility values are calculated from the GEMINI trials irrespective of the treatment arms. Please provide utility values by treatment arm. Furthermore, please provide confidence intervals (CI) for utility values for the pooled data, and by treatment arm.

B41. On p page282 (Table 7.4.3.1) the utility value from GEMINI II (maintenance) in the overall population with mild-moderate disease is 0.73, but is 0.72 for moderate disease and 0.70 for severe disease. Please check the values reported in this table.

B42. In the SA and PSA, utility values are sampled from a beta distribution, assuming N=100. Please clarify why the CI were not used in the SA and PSA?

B43. The company assumed the utility value while in the surgery health state to be the same as for patients in the moderate to severe disease health state. Please clarify the

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rationale for this assumption. Furthermore, please clarify why the utility value used in Bodger et al (2009) was not used instead?

B44. The company used decrement in utility estimated from different sources. Please clarify the method used to estimate these decrement in utilities, notably the instrument and valuation used (EQ-5D, general population, TTO). Please clarify whether the method and instrument used are comparable to utility values estimated from the GEMINI studies?

B45. On page 296 (Table 7.4.9.2), please clarify the assumption on the duration assumed for the decrement in utility values.

Mortality

B46. **Priority:** It is assumed that patients with Crohn's disease are at increased risk of death and a hazard ratio (HR) is applied to general mortality according to the severity of the disease. Please provide the sources used to estimate these risks and clarify why particular values were used for particular health states.

B47. Please explain why the mortality rate associated with surgery is estimated from a HR rather than directly from results of the 'targeted review'?

Patient population

B48. **Priority:** On page 205, the company states that the population is moderate to severe (CDAI score 220 to 600) to reflect the license of vedolizumab. However, no reference to such threshold was found in the SPC. Furthermore, the trial only included patients with a CDAI score up to 450. Please state which section of the marketing authorisation for vedolizumab defines people with moderate to severe Crohn's disease as people with aCDAI score between 220 and 600.

B49. Patient characteristics in the economic model are derived from a range of sources. Please clarify how these studies were selected. Please provide a comparison with trial data from the GEMINI trials.

Other

B50. **Priority:** On page 217, several values are missing. Please provide the missing values.

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B51. **Priority:** Please provide data from the GEMINI trials on the proportion of patients who had undergone surgery (by treatment arm).

B52. On page 184, the company reports that 19 records were included (5 economic evaluations, 16 utility reviews and 5 cost and resource use reviews). Please confirm that these are not mutually exclusive?

B53. On page 225, the company conducted a SA using a value of 0.072 for surgery. Please provide the source for this value.

B54. On page 231, the company states that clinical experts reviewed a model specification document that outlined the structure of the model and the proposed calculations. Later on, the company states that the clinicians were then asked to review the final version of the model technical report and provide written comments, thereby validating the model assumptions. Please clarify the difference between the model specification and technical report. Furthermore, please clarify the role of experts consulted. Finally, please provide the name and expertise of experts consulted.

B55. The SPC states "The recommended dose regimen of Entyvio is 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter. Patients with Crohn's disease, who have not shown a response may benefit from a dose of Entyvio at Week 10". Please clarify why the base case economic model uses assessment at 6 weeks rather than assessment at 10 weeks.

Section C: Textual clarifications and additional points

C1. Surgery searches. These searches are reported, but the results of the review not reported. Surgery does not seem relevant to the decision problem as defined in the NICE scope. Please clarify why these have been included.

C2. Figure 6.2.2.1 and 6.2.2.2 (PRISMA diagram). Some text is missing e.g. from the box “additional articles”. Please check both diagrams and provide any missing text.

C3. Figure 6.3.2.2 – should this read Gemini III (rather than Gemini II)?

C4. Pg 80 – suspected typo in the primary outcome text for Gemini III. Please provide correct text.

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C5. Pg 93 & 94 – 9 subgroup analyses are mentioned in the table, but only 8 listed on page 95. Please clarify

C6. Figure 6.7.3.4 – which Sandborn reference? A or b?

C7. In p222, there appear to be a typo in the following sentence: “In addition, it is assumed in the model that treatment with a biologic (Vedolizumab, Infliximab or Adalimumab) is limited to one year and all patients on therapy at week 5 of the model switch to conventional treatment”. Please clarify whether this should say 52 or 54 instead of 5.