NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Single Technology Appraisal (STA)

Naloxegol for treating opioid induced constipation [ID674]

Dear Zavy

The Evidence Review Group, Kleijnen Systematic Reviews Ltd, and the NICE team have now had an opportunity to take a look at the submission received on the 5 November 2014 by AstraZeneca. 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 NICE team will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm**, **Friday 12 December 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 focus on responding to the main questions first. However, please note we have designated some questions as lowest priority (questions 76 to 82). We would appreciate if you could respond to all the clarification questions in the timescale above.
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 Richard Diaz, Technical Lead Richard.Diaz@nice.org.uk. Any procedural questions should be addressed to Lori Farrar, Project Manager Lori.Farrar@nice.org.uk in the first instance.

Yours sincerely

Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

1. Please provide an overview of all KODIAC trials, including the study design, details on the PICO and the follow-up period as well as reasons for exclusion from the submission, if applicable.
2. **Priority request:** Please provide additional details on KODIAC 4 and 5.
   a) How many patients in each arm of the KODIAC 4 and 5 studies were from the UK and the US?
   b) Please specify which laxatives patients have failed previously. Do these include dietary fibre and lubricant agents (mineral oil)?
   [redacted]
   d) Please provide the number of bowel movements (BMs) for each arm in KODIAC-4 and 5, with and without rescue remedy, for the intention-to-treat (ITT), laxative inadequate response (LIR) and inadequate response to 2 laxatives (2xLIR) populations.
   e) Please specify how many patients received the maximum dose of bisacodyl in KODIAC 4 and 5 for the ITT, LIR and 2xLIR populations, by treatment arm.
3. Please confirm that all references have been correctly referenced. We noticed that references 2 and 3 are missing, i.e. the first reference is (1) followed by (4). Please clarify for example, if this is caused by deleting these references without updating the reference list accordingly?
4. The following reference was not in the reference pack and should be provided:
   - Coyne K, Margolis MK, Wilson H, Thompson C, Chen J. Final report for longitudinal study of patients with opioid-induced constipation (12AST11894/A-12292.333). 2014
5. On page 27, it is described that another study (KODIAC 6) had to be terminated due to "severe recruitment difficulties". Please describe these difficulties in more detail.
6. Page 28 describes that *"Naloxegol will only be contraindicated in the following patients with cancer pain:*
   - *Patients with underlying cancer who are at a heightened risk of gastrointestinal (GI) perforation, such as those with;*
     - *underlying malignancies of the GI tract or peritoneum*
     - *recurrent or advanced ovarian cancer*
     - *vascular endothelial growth factor inhibitor treatment"*

   Please provide the evidence for this statement or a draft EPAR if it includes the requisite information.
7. On page 31 of the submission, the company states "Naloxegol should be prescribed with caution in patients with clinically important disruptions to the blood brain barrier

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(e.g. advanced Alzheimer's, active multiple sclerosis, CNS metastases, primary brain malignancies etc.)." Can you provide references for this statement? Are data on these groupings captured?

8. **Priority request:** Rectal intervention is included in the scope as a comparator, but has not been included as a comparator in the submission. Please clarify the rationale for the decision not to include this as a comparator.
9. **Priority request:** Please explain why the definition of 'inadequate response to laxatives' in the submission differs from the definition of 'inadequate response to laxatives' in previous NICE technology appraisals: "Treatment with at least two laxatives from different classes, at the highest tolerated recommended doses for at least 6 months has failed to provide adequate relief." [1-3]
10. On page 47 of the submission, it states that [redacted] However, the referenced document states that 10 clinicians out of 34 agreed. Please provide an explanation for the statement on page 47.
11. On page 39 of the submission it states that "For patients who experience severe/persistent/worsening GI adverse events, consideration may be given to reducing the dose of naloxegol to 12.5 mg".
    - What proportion of patients experienced these adverse events in the KODIAC trials, and how many patients had dose reductions because of this or because of other reasons?
    - Please explain whether this was taken into account in the model and, if not, provide a rationale for this (both in terms of costs and in reduced effectiveness of naloxegol in these patients).
12. Please confirm that the LIR population refers to all patients randomised with these characteristics (i.e. inadequate-laxative-response within ITT population).
13. Please clarify how long patients need to have been continuously on opioids to be eligible for treatment with laxatives?
14. Is rectal intervention permitted within the care profile of those defined as laxative intolerant and hence eligible for naloxegol or does the period on treatment start again after rescue medication has been implemented?
15. Please clarify whether switching within class of laxatives is permitted prior to designation of laxative intolerance. Is it possible that one laxative in the same class as another can be more effective?
16. **Priority request:** On page 37 of the submission, it states: *"…In the absence of RCT data demonstrating the head-to-head efficacy of naloxegol versus laxatives, trial data from KODIAC 4 and 5 comparing spontaneous bowel movements (SBMs) – those BMs that occurred without the need for rescue medication (bisacodyl) in the last 24 hours – with total BMs in the placebo plus rescue bisacodyl arm – those BMs that occurred as a result of rescue bisacodyl – will be used as a proxy for stimulant laxative used PRN. An additional analysis comparing total BMs in the naloxegol plus rescue bisacodyl arm with total BMs in the placebo plus bisacodyl arm will*

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demonstrate the effectiveness of naloxegol when used in combination with stimulant laxative used PRN." Please clarify the following:

a) Is response according to any bowel movement (BM) used as an outcome for any treatment/treatment arm/comparator?
b) If it is then:
   - which treatments/treatment arm/comparator is it used for
   - which analyses i.e. for clinical effectiveness, cost effectiveness or both?
c) Is the effectiveness of naloxegol plus bisacodyl estimated using spontaneous bowel movement or BM in the definition of response?
d) Can the company confirm that there is no data on the response to any laxative other than bisacodyl e.g. senna, either in the form of a trial vs. placebo or vs. bisacodyl in a similar population?

17. According to page 218, "Senna is the most commonly used stimulant laxative in the UK".
    a) Are there any studies comparing the effectiveness of bisacodyl compared with senna?
    b) If so, please describe and explain why these studies were not considered relevant by the company?
18. **Priority request:** Bisacodyl is used as a proxy for laxatives; therefore, please provide clinical trial data for bisacodyl:
    a) What is the relative effectiveness of bisacodyl compared with other laxatives?
    b) Please confirm whether any systematic searches were conducted to identify other trials which could have contributed to indirect and/or mixed treatment comparison (page 214), e.g. laxatives vs. placebo? If none were conducted, please provide a rationale for this approach?
19. Please explain why a "wash-out period" was not reported for the trials? A wash out period and is used in trials to ensure that no latent effect of earlier treatment contaminates the results in a trial situation[3] Please explain if a wash out period was considered to be unfeasible or unwarranted.
20. How was "usual care" defined in KODIAC 8 (page 46)?
21. **Priority request:** Please provide a list of the 26 studies excluded for section 6.1 (according to figure 2).
22. On page 72, a subpopulation of patients is described as having "an inadequate response from at least 2 classes of laxatives for ≥4 days in the 2 weeks prior to study entry or reported unsatisfactory laxation from ≥1 additional laxative class from the 6 month OIC history prior to screening".
    a) Please provide details on length of the period of opioid use for the included trials?
    b) Explain whether there is a minimal period of opioid use for the eligible population in the trials .If there isn't, please state the reasons.
    c) Provide frequency distributions of opioid usage for the trials.
23. Table 5 lists the *"Naloxegol Phase II"* trial which included *"Adult OIC patients with non-cancer or cancer-related pain"*. However, according to section 10.10.6 *"treatment with opioids for cancer-related pain"* was excluded. In addition, figure 2 lists 5 studies that were excluded due to "malignant pain".
    a) Please explain these discrepancies.

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b) If cancer-related pain was included, please provide results for this subgroup.

24. Table 6 lists one *"relevant non-RCT"*. Please justify the inclusion as the population is outside the scope.
25. **Priority request:** Page 73 lists an additional subgroup (2xLIR). The 2xLIR population is closer to NICE's definition of inadequate responders. Given this, please provide further clarification for why you did not provide the same data for the 2xLIR population as for the LIR population, and the same analyses (meta-analyses, and network MA) and economic model in the submission?
26. On page 77, there is a discrepancy between the second bullet point ("5.3%, 9.2%, and 2.5% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively") and the following text ("Discontinuations as a result of adverse events occurred in 5 (4.3%), 11 (9.2%), and 3 (2.5%) patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively."). Please clarify which statement is correct?
27. Please provide further details, e.g. frequency count, on the days *"patients had taken more than one laxative class for at least 4 days in the two weeks prior to baseline..."* (Page 78).
28. Table 39 lists *"History of chronic constipation"* as a key exclusion criterion for the BOI study. Can you please explain why this was done and why this study is still relevant?
29. Table 189 is entitled *"Profile of Opioid Use for Naloxegol 25mg"* but has *"exclusive use of morphine"* at 100% and exclusive use of oxycodone at 100%. Please provide an explanation for the inclusion of this table and its reported values.
30. EMA states that *"On 25 September 2014 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Moventig, 12.5 mg and 25 mg, film-coated tablet intended for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s)".* Did EMA provide a definition of what was meant by *"an inadequate response to laxative(s)"*? Please provide the definition if possible.

<u>Section B: Clarification on Meta-analysis and Mixed Treatment Comparison</u>

31. Page 127 states that *"Direct meta-analysis of the two included RCTs evaluating methylnaltrexone compared with placebo was not undertaken due to dosing differences (one study of subcutaneous methylnaltrexone and one study of oral methylnaltrexone)".* Please explain why these 2 studies could be combined in the MTC analyses section 6.7.2.
32. According to page 127, 2 of the naloxone trials were also excluded due to reporting of results at different timepoints. These studies were evaluated separately. Please explain why these two 4/5-week studies were combined in the MTC analyses in section 6.7.2 and compared with 12-week studies for naloxegol.
33. **Priority request:** Given the limited number of trials included in the direct comparison meta-analysis (page 128), please provide a rationale for the random effects empirical based methods and present forest plots for all meta-analyses.
34. **Priority request:** Table 56 presents *"DIC values for random vs fixed effects models"*. *"Based on the results of the DIC analysis, a random effects model was chosen over a*

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M1 4BT
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fixed effects model". Please provide a rationale for choosing the random effects model considering table 56 indicates smaller (i.e. better) DIC values for the fixed effects model.

35. For section 6.7:
    a) Did the non-naloxegol studies include the relevant population (anticipated license)? Please define these populations if possible.
    b) Please provide complete study characteristics for all included studies (by treatment arm) in the MTC: Methodology, see Table 7; Eligibility criteria, see Table 8; Characteristics of patients, see Table 9 and 10; Outcomes, see Table 11; Analyses, see Table 12; Participant flow, see Fig 4 and 5.
36. Section 7.3.1, tables 90 and 92 (MS page 245) show the response rates for naloxegol based on the trial and the MTC. This shows a clear difference. Please confirm that response for the MTC analysis is the same as the model definition of response (as opposed to the clinical effectiveness definition of response)?
37. **Priority request:** Please provide a full MTC analysis for the model including placebo, placebo plus bisacodyl and naloxegol plus bisacodyl, i.e. please expand the current MTC to include all comparators.

<u>Section C: Clarification on cost-effectiveness data</u>

38. The economic analysis is based on the premise that the eligible population has failed on a single laxative. This means that switching of treatments (other than to defined comparators or the intervention) is not an issue. [redacted][4]). It would be useful if the company could consider the impact of permitted switching between different treatments which would also help place naloxegol at the most cost-effective position in the care pathway.
39. **Priority request:** In the CSRs of KODIAC 4 and 5 (pages 104 and 106, respectively) it states: *"A complete analysis of the EQ-5D to calculate QALYs to support health economic analyses for payers is reported separately."* Please provide these reports.
40. On page 23, you state that *"Results are also presented for naloxegol 25 mg plus bisacodyl to demonstrate the cost-effectiveness of naloxegol when used in combination with a stimulant laxative. This scenario is considered most clinically relevant given the multifactorial nature of constipation and clinical guidance obtained via an advisory board and AstraZeneca sponsored research"*.
    a) Please clarify how this clinical guidance was identified (consensus, majority etc.)?
    b) In light of this statement, please comment on the most appropriate choice for the base case in the cost-effectiveness model? The statement suggests that naloxegol 25 mg vs. placebo is not the best choice for the base case.
41. **Priority request:** In the section 6.5.4, page 88, table 17 and page 89, table 18 shows that the response rate of naloxegol differs between LIR and non-LIR patients, while the response rate of placebo is more or less similar between LIR and non-LIR patients. Consequently, the efficacy of naloxegol differs between the LIR and non-

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LIR population. In anticipation of the license, the cost-effectiveness analysis is restricted to the LIR population. Please provide the inputs and results of the cost-effectiveness analyses for all patients with OIC irrespective of response to previous laxatives as well as for the 2xLIR patients.

42. **Priority request:** Please provide the details of the methodology of all surveys conducted to obtain resource use data, populate and/or validate the model (GP Omnibus, 29 clinician, Advisory board, 3 KOLs) & BOI data in appendices? Please consider the following sub-questions when providing your answers:
    a) Specific information about the advisory meeting as described in section 10.24 is missing. Please provide more detailed information about the questions asked during the advisory meeting held on July 16-17, 2014.
    b) Please specify if experts participated in more than one survey/meeting(s)?
43. Section 7.2.2 on page 237: it is mentioned that "Patients in the 'OIC' and 'non-OIC (untreated)' states use rescue therapy (e.g. laxatives) as required, with the laxative use in the 'non-OIC (untreated)' state being prophylactic." Please clarify how the laxative use in non-OIC (untreated) can be rescue therapy and prophylactic at the same time.
44. **Priority request:** Please explain why throughout the health economic analyses data have been pooled from KODIAC 4 and 5 rather than performing meta-analyses.
45. Please specify the y-axis (i.e. the measure of differences) on the graph in section 7.3.7 on page 252, figure 17, and explain the inclusion (in the key of the chart) of non-OIC (on treatment) patients (late responders) in this comparison:
46. In section 7.3.7, please provide diagnostic plots (cumulative log-hazard) with both treatment groups in one plot. Please explain why the same parametric function was chosen for naloxegol and placebo and provide the results of the statistical tests (or graphs) that justify the assumption of proportional hazards in the health economic model.
47. In section 7.3.7, please provide more detail about the procedure to get to the per-cycle probabilities and whether the face-validity of these probabilities been checked with clinical experts.
48. Please provide the following reference as referenced in section 7.4.2, page 264 of the submission:
    - Bell T, Annunziata K, Leslie JB. Opioid-induced constipation negatively impacts pain management, productivity, and health-related quality of life: findings from the National Health and Wellness Survey. J Opioid Manag. 2009 May-Jun;5(3):137-44.
49. Please provide more information about the differences in quality of life between patients with and without OIC as this is not described in the poster by Annunziata et al.[5].
50. **Priority request:** Different definitions of OIC status have been used in the trial and in the model. Please clarify which definition was used to define OIC in the context of the utility analyses.
51. **Priority request:** The distinction in utilities between treatment and time is based upon an analysis using the change in utility score as the dependent variable (Table 103, page 266). Since the economic model does not specifically incorporate the

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change in utility, but the utility values itself, please provide a rerun of the analysis, now using absolute utility rather than change in utility as the dependent variable.

52. The random mixed effect model includes OIC as an independent variable. Please clarify at what time point this OIC status was measured.
53. **Priority request:** Please provide more details regarding the model selection as seen in table 103, e.g.
    a) How was this model selected and which covariance structure was assumed?
    b) Were other interactions included?
    c) Please also show the results including all interaction terms.
    d) Additionally, can you please provide a test of the selected model versus a model without interactions?
54. Table 106 describes non-treatment specific inputs for OIC and non-OIC. Please explain why the utility of the OIC state is different to the utility of the OIC state as reported in Table 104 and 105. Please specify for table 106 the source in a similar way as in table 104 and 105.
55. An alternative tariff has been used in a scenario analysis (MS page 269) with the argument that the underlying condition might cause patients to be in the worst health state and that the HRQOL is also evaluated without an additional decrement of being in the worst health state. Two questions arise with this assumption:
    a) Patients with OIC almost certain have an underlying condition which influence HRQOL. The exclusion of the effect of this underlying condition means that only a specific aspect of HRQOL is measured instead of an overall assessment of HRQOL. Since the goal is to have a generic assessment of HRQOL including comorbidities and side effects, please further justify the rationale for using this alternative tariff.
    b) The Wittrup-Jensen tariff is a Danish tariff and within their study five health states were explicitly compared using the Danish and UK tariff. It was shown that in all these five health states, the Danish tariff resulted in larger utilities. Please provide the justification for why this tariff could be used in the UK population.
56. Table 109 shows the results of quality of life estimated from the literature. The quality of life is separately reported for OIC and non-OIC. However, the definition of OIC differs from the definition used in the economic evaluation. In the study of Penning van Beest et al. [6], OIC is defined according to patient responses regarding constipation and the use of laxatives. As it is therefore questionable whether the OIC group of this study is comparable with the OIC group in the economic evaluation, please provide more justification for using the utility of this study in a scenario analysis.
57. Inclusion criteria of the systematic review of health-related quality of life data state that studies were restricted to patients with OIC. Please provide evidence that the quality of life in chronic constipation patients is different from the quality of life in OIC patients? If there is no difference, including studies evaluating quality of life in chronic constipation patients may increase the evidence base regarding quality of life, since only 6 studies were included in the review of HRQOL.
58. Section 7.4.7 states that the utility inputs in the model were broadly similar to the utility values derived from the literature search, though it seems that the utility values

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used as inputs are consistently larger than the utility values in the literature. Please explain why these values should be considered as broadly similar.

59. In section 7.4.8, it is stated that the utility impact of AEs is captured by treatment-specific utility inputs. However, treatment-specific utility inputs were only used in the comparison of naloxegol with placebo (+ bisacodyl). Please explain why no utility impact of AEs was assumed in the comparison of naloxegol versus MNTX and OXN.
60. **Priority request:** Section 7.5.3 “No systematic search for resource use was completed. Clinicians were consulted to estimate the resource use associated with the management of constipation and associated adverse events for use in the economic model”. Please explain why no search was conducted and why other professional groups, like nurses were not consulted.
61. Section 7.5.4 Please provide all the details regarding the clinical experts as requested in the template.
62. Page 287 (section 7.5.7). The mean expected cost per AE was calculated as the weighted average of patients with Grade 3/4 events (and the corresponding unit cost) and patients with Grade 1/2 events (at a cost of £0). These costs were then summated to provide an overall total AE costs. However, no data is provided regarding the rates at which Grade 3/4 events and Grade 1/2 events occur to track the calculations. Please provide these data.
63. **Priority Request:** Section 7.6.2. In the DSA, parameters are varied by ± 20%. However, the reported range could in reality be much larger or smaller for each parameter when confidence intervals (CI) are taken into account. Please provide a DSA with ranges based on 95% CI (instead of ± 20%).
64. In section 7.7.2, figure 23 shows the number of patients in each health state over time for naloxegol. Was the assumption that all patients will be off naloxegol after 30 cycles verified by clinical experts?
65. Sections 7.7.5 & 7.7.6(pages 297 and 298 of the MS): Could you please provide reasons why total costs of naloxegol (25mg) were £1,202 (table 122) and the same costs were £1,272 (table 123)? Furthermore, these differences in reporting are reflected on incremental cost differences as £185 and £256, respectively.
66. Section 7.7.9 on page 312, table 132: Resource use of costs of managing constipation (in LIR population) indicates that differences in the GP omnibus survey (which was used in the base case) and BOI data (which was used in the scenario analyses) was 10 fold. Could you please explain the rationale of using GP omnibus survey values in the base case rather than the BOI? For example, which study provides a good proxy for quantification of costs of managing constipation in LIR population in the model, especially when clinical practice in the UK is considered?
67. Section 7.7.9: Please provide the methodology on GP omnibus survey, as it is not included in any of the appendices.
68. Section 7.8.1: The methods used to externally validate the model are very limited.
    a) Did experts validate the face validity of the results?
    b) Please provide a report about the technical validation that was performed externally.
69. Section 10.10.6 on page 383. Was a language restriction applied in the screening of the cost-effectiveness studies?

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70. Section 10.25, table 183: Distribution of adverse events by treatment arm. Please specify the grade of listed adverse events in this table.
71. Section 10.28, appendix 26: Calculation of average age of cancer pain patients in the model was 72 years which was derived using data from the Office for National Statistics (ONS) for registrations of newly diagnosed cancer cases in England. On page 218: section 6.10.4, the mean age of cancer patients was indicated to be 70 years. Please provide clarification regarding the mean age of cancer patients used in the model.

Section D: Literature searches

72. **Priority request:** On page 47 you state that the systematic review conducted in October 2013 was an update to an existing 2008 Cochrane review, but provide no reference. Please confirm if the review you are referring to is:
    - McNicol ED, Boyce D, Schumann R, Carr DB. Mu-opioid antagonists for opioid-induced bowel dysfunction. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006332. DOI: 10.1002/14651858.CD006332.pub2. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006332.pub2/abstract
73. **Priority request:** According to page 47, "Laxatives were not included in this update as there was a lack of recent data and head to head studies versus naloxegol identified in the initial searches. It was therefore considered unlikely that any new data for laxatives would be available". Please provide more details justifying this approach.
74. **Priority request:** Please confirm if the searches reported in section 6.8 (non-RCT) and linked section 10.6 were also screened to identify papers of interest to other sections i.e. RCTs and Adverse Events.
75. **Priority request:** Please confirm that the strategies reported in section 10.2 are the correct searches as they do not appear to match the search flow depicted on page 53.
    If these are the correct searches:
    a) Please provide clarification as to what the searches in 10.2 intended to retrieve and any additional strategies used for identifying papers on the required comparators for sections 6.1 and 6.7
    b) Page 47 mentions a range of searches used to inform this review, including update searches for the 2008 Cochrane review. The searches detailed in appendix 10.2 do not appear to match all those detailed on page 47. Please provide all relevant strategies.

Lower priority questions:

76. Page 20 refers to the *"key KODIAC trial"*. Please state which of the KODIAC trials you are referring to and provide a reference for this.

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77. According to table 3, only English language studies were included. Please justify this approach.
78. Figure 3 does not include reasons for exclusions for references excluded at 2nd pass. Please provide these reasons for exclusion.
79. Table 7 state that 167 sites were used for KODIAC 5. However, the detailed numbers in the same table do not add up to 167. Please provide the correct numbers.
80. Regarding the Medline search reported in 10.2:
    a) Whilst 10.2 states that this was run on Ovid, both the search flow on page 53 and the syntax reported would suggest that this is a Pubmed search. Please provide clarification.
81. The ERG are unclear regarding whether the first set of terms in each search line of the Medline strategy are MeSH or freetext, as these details don't appear in the strategy.
    a) Is this a formatting error?
    b) Please could you prove a clean copy of this strategy?
82. Please explain the rationale of limiting the searches described in section 7.4.5 (HRQL) and detailed in section 10.12 to English language only and discuss what effect this may have had on your results.

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City Tower
Manchester
M1 4BT
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REFERENCES

[1] National Institute for Health and Care Excellence. Clinical Knowledge Summaries: Scenario: Constipation in adults. 2014 [accessed: 25.11.14]. Available from: http://cks.nice.org.uk/constipation#!scenario

[2] National Institute for Health and Care Excellence. *Prucalopride for the treatment of chronic constipation in women: NICE technology appraisal guidance 211 [Internet]*. London: NICE, 2010 [accessed: 25.11.14] Available from: http://www.nice.org.uk/guidance/ta211

[3] National Institute for Health and Care Excellence. *Lubiprostone for treating chronic idiopathic constipation: NICE technology appraisal guidance 318 [Internet]*. London: NICE, 2014 [accessed: 25.11.14] Available from: http://www.nice.org.uk/guidance/ta318

[4] AstraZeneca. Consolidated defintion of laxative inadequate response. Data on file [As referenced in company's submission].

[5] Bell T, Annunziata K, Leslie JB. Opioid-induced constipation negatively impacts pain management, productivity, and health-related quality of life: findings from the National Health and Wellness Survey. *J Opioid Manag* 2009;5(3):137-44.

[6] Penning-van Beest FJ, van den Haak P, Klok RM, Prevoo YF, van der Peet DL, Herings RM. Quality of life in relation to constipation among opioid users. *J Med Econ* 2010;13(1):129-35.