Dear Joao,

In response to the issues raised by Novartis and the Royal College of Physicians (RCP) in their responses to the Appraisal Consultation Document (ACD), we would like to make the following points. We appreciate that as this is a written response, you may need to make this document public if requested for this information.

Firstly, with regard to the RCP response:

Our interpretation of the appraisal objectives
We wish to point out that the appraisal objectives as stated in both the draft and final scopes for this review stated clearly that the objective was to:
"appraise the clinical and cost effectiveness of imatinib within its licensed indication for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours **which have progressed on treatment at a dose of 400 mg/day**".[1 2] Thus, the ERG report concentrated on those progressing at a dose of 400mg/day and hence would disagree that this is a restrictive interpretation of the review objectives.

We also note that the RCP were consulted on the development of the scope for this appraisal and state: "The nature of the problem is well described, i.e. GIST progressing after a period of time on imatinib 400 mg daily".[3] However, both scopes indicate that the original remit from the Department of Health/National Assembly for Wales was "To appraise the clinical and cost effectiveness of imatinib in its licensed indication for the treatment of gastro-intestinal stromal tumours". This was altered before the draft scope was issued by NICE, but the ERG are not aware of the reasons for this change.

The 600mg/day dose was included as an intervention in the scope, which NICE consulted on and the possibility of its clinical irrelevance was not noted by consultees at that stage. It was therefore necessary to include this dose in the assessment report. In revisions to our ERG report following peer review we have added additional comments on this as we appreciate that some of the care pathways are more plausible than others.

Data on the effectiveness of imatinib for those patients without CD117 expression were not considered as the scope population is stated as "People with KIT (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST) whose disease has progressed on treatment with imatinib at a dose of 400 mg/day". Methods for diagnosing GIST were not part of the objectives for this appraisal, although the ERG report does make reference to PDGFRA and DOG1 in the background section (page 2).

Included and excluded evidence
The reasons for exclusion of the Meta-GIST data were discussed at the first Appraisal Committee meeting. This is noted in section 4.3.4. and relates to the appraisal objective (above) of considering only those patients who had progressed on the 400mg/day dose.

The Debiec-Rychter paper referenced in the RCP response was included in our ERG report. Only p-values were reported for the population of interest. Page 32 of the ERG report therefore states that this study showed that response following crossover to the 800mg/dose was significantly more likely to occur in patients with wild-type GIST than exon 11 mutation (p=0.0012) and also significantly more likely to occur in exon 9 mutation compared with exon 11

mutation (p=0.0017). This information was presented during the 1st Appraisal Committee meeting and is noted in section 4.1.8 of the ACD.

Page 19 of the ERG report makes reference to study A6181112 but no published data were available for this trial.[4]

With regard to imatinib blood level testing, thresholds for imatinib blood levels were not a stratification factor for this review because none of our included studies reported them, and the studies that did report this outcome did not meet the inclusion criteria for this review for other reasons. However, we do appreciate it could be a clinically important factor in terms of the decision to dose escalate, and also that it may have an impact on the model in terms of cost-effectiveness with regard to the timing of costs and benefits and the subsequent discounting required.

Economic Model

The majority of the population (>80%) in the randomised controlled trial considered in TAR179 had predominantly progressed on previous doses of imatinib >400mg/day. As this appraisal was concerned with those progressing on the 400mg/day dose, the study populations are different. Very sparse data were available for those progressing on the 400mg/day dose, and so it is repeatedly stated in the ERG report that the results are surrounded by considerable imprecision and are potentially unreliable (see pages 69, 70, 81, 89, and 90 of the ERG report). We also note that the sensitivity analyses reported for TA179 provide estimated ICERs in excess of the £272,365 figure in our ERG (see page 90 of TAR179).[5] This illustrates the considerable uncertainty that surrounds the estimates of cost-effectiveness, which in the case of TA179 were caused by differing methods of estimating hazard ratios, and assumptions about whether the NHS would incur the first cycle costs of sunitinib.

With regard to utility scores, data on the quality of life for people who had progressed on 400mg/day were sparse. The 0.935 score for imatinib was taken from the previous HTA.[6] As pointed out, this may be too high for patients who have already progressed. Should this utility value be reduced and other utilities remain unchanged, then the ICER of any treatment compared with best supportive care will increase. However, it would be expected that the quality of life of those who progress after further treatment would then also be lower than the 0.577 used in the model.[7] The net impact of reducing both pre and post-progression utility scores is uncertain, and depends on the magnitude of the absolute reduction in both scores. We anticipate that there may be a floor effect for utility following further progression. If this were the case, it is more likely that the absolute difference between utility scores pre and post-progression would be reduced. The impact of this might be expected to be an increase in the ICER. Table 20 of the ERG report sensitivity analysis (page 78) explores the impact of increasing or decreasing the absolute difference between pre and post-progression utility.

Secondly, with regard to the Novartis submission:

The statement made by Novartis regarding section 4.1.7 of the Appraisal about the study by Park et al is misleading as the ERG report indicates that 5/12 patients given an escalated dose of 600mg/day imatinib showed either partial response or stable disease, whereas 4/12 patients given an escalated dose of 800mg/day showed either partial response or stable disease. Therefore the comment that actually "nine patients achieved either partial response/stable disease, not four" refers to ALL escalated doses, and not solely the 800mg/day dose. The ACD should not be changed as the point refers only to the 800mg/day population.

In addition, their comment response to section 4.3.5 of the report "There were only two studies in which the dose of imatinib was increased from 400mg to 800mg (EORTC study and S0033)" is also incorrect as the Park et al study also reported that 12 patients received an escalated dose of 800mg imatinib following a 400mg dose.[8]

The comment on section 4.1.20 relates to discrepancies on the number of people requiring a dose reduction of imatinib within the EORTC-ISG-AGITG trial. The figure of 70% quoted actually relates to the population no longer following the study protocol, whilst our population of interest is the 133 patients who crossed over to high-dose imatinib according to the study protocol. It is stated on page 1753:
"...in those patients crossing over to high-dose imatinib but not according to study protocol, 70% did not require a dose reduction. The remaining analyses in this report are based on the 133 patients who crossed over to high-dose imatinib according to the protocol recommendations".[9]
Therefore the figure of 31% in the ACD should be retained.

We hope these comments help clarify these issues in advance of the 2nd Appraisal Committee meeting next week.

Yours sincerely

[redacted]

References:

1 National Institute for Clinical Excellence. Health Technology Appraisal. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (part review of Technology Appraisal No. 86). Draft Scope. Available at: http://www.nice.org.uk/nicemedia/live/12180/44750/44750.pdf

2 National Institute for Clinical Excellence. Health Technology Appraisal. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (part review of Technology Appraisal No. 86). Final Scope. Available at: http://www.nice.org.uk/nicemedia/live/12180/45261/45261.pdf

3 National Institute for Clinical Excellence. Health Technology Appraisal. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (part review of Technology Appraisal No. 86). Comment 1: the draft scope. Available at: http://www.nice.org.uk/nicemedia/live/12180/45262/45262.pdf

4 Safety And Effectiveness Of Daily Dosing With Sunitinib Or Imatinib In Patients With Gastrointestinal Stromal Tumors. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00372567?term=a6181112&rank=3

5 Bond M, Hoyle M, Moxham T, Napier M and Anderson R. The clinical and cost-effectiveness of sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer. Available at: http://www.nice.org.uk/nicemedia/live/12040/43430/43430.pdf

6 Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J et al. Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation. *Health Technol Asses* 2005;9:1-142

7 Chabot I, LeLorier J, Blackstein ME. The challenge of conducting pharmacoeconomic evaluations in oncology using crossover trials: The example of sunitinib for gastrointestinal stromal tumour. *Eur J Cancer* 2008;44:972-7

8 Park I, Ryu MH, Sym SJ, Lee SS, Jang G, kim TW et al. Dose escalation of imatinib after failure of standard dose in Korean patients with metastatic or unresectable gastrointestinal stromal tumour. *Jpn J Clin Oncol* 2009;39:105-10

9 Zalcberg JR, Verweij J, Casali PG, Le Cesne A, Reichardt P, Blay JY et al. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. *Eur J Cancer* 2005;41:1751-7