31st August 2012

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Dear [redacted],

Re: Single Technology Appraisal – Eltrombopag for the treatment of chronic immune thrombocytopenic purpura (cITP)

The Evidence Review Group (Aberdeen HTA Group) and the technical team at NICE have now had an opportunity to take a look at the submission received on 10th August 2012 by GlaxoSmithKline. 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 **17:00, 14th September 2012**. 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 Scott Goulden – Technical Lead (scott.goulden@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell – Project Manager (Jeremy.Powell@nice.org.uk) in the first instance.

Yours sincerely

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1: priority question

Pages 38-39. At present it is difficult to compare the numbers in the flow diagrams with those reported later in the text and tables of the submission. For example the PRISMA diagram suggests that 108 TPO-RA studies were included in the review. However, information on page 107 suggests that 116 of such studies were included (79 later excluded and 37 included and listed in Table B41).

Please provide the total number of included and excluded studies from both the original and the updated literature search, the total number of included studies according to the type of intervention (i.e. eltrombopag; romiplostim; non-TPO-RA). Within each intervention category please state the number of randomised and non-randomised studies (see Appendix A Figure 1). Please also clarify how many publications relate to the identified studies and whether you consider multiple publications as separate studies?

A2: priority question

Page 41 and pages 84-85. Tomiyama 2009, Shirasugi 2011 and Shirasugi 2009 were all excluded as they included only Japanese patients. However, the pre-specified inclusion criteria for the review do not justify their exclusion (i.e. all eltrombopag RCTs included a large proportion of people of Asian origin). Please justify the exclusion of Tomiyama 2009, Shirasugi 2011, and Shirasugi 2009 studies. The reference for the Tomiyama 2009 study in Table B6 is a conference abstract. However, this trial - funded by GlaxoSmithkline - is now published in full. Please clarify the exclusion of these data from further discussion and analyses.

A3: priority question

Please clarify the approaches used to handle dropouts/non-adherence in TRA 100337A, TRA 100337B, and TRA 102537 RAISE. Were the same approaches used to derive the meta-analysis data or were there efforts to ensure that dripouts/non-adherence was handled consistently across the studies?

A4: priority question

Page 74 Table B22. Please comment on how comparable the ‘sustained response’ for eltrombopag and the ‘overall response’ for romiplostim are. Please explain the difference between the “subjects treated for >6 months” and “ITT” columns.

A5: priority question

Page 79. The six week platelet response rates from the three eltrombopag trials (TRA100773A, TRA100773B and RAISE) were combined in a meta-analysis to obtain an ‘‘overall’’ Eltrombopag treatment effect compared with placebo. Meta-analysis was conducted only for a single outcome: platelet response at 43 days. However, other outcome data were collected by more than one study, e.g. bleeding (WHO scale) and SF-36. Why were bleeding rates and SF-36 scores not meta-analysed between Eltrombopag studies?

A6: priority question

Pages 94 and 101. Please explain why TRA100773A and TRA100773B were not included in the indirect comparison given that they collected information on response and bleeding? The mean daily dose of eltrombopag levelled out in RAISE at around

6 weeks, considering that TRA100773A and TRA100773B lasted for 6 weeks, does this not provide justification for their inclusion?

A7: priority question

Page 101. Please confirm whether '3.14' in Table B37 is correct . Also, please explain the footnote referring to 'inconsistency in handling of zero events'.

A8: priority question

Page 107. Please clarify if and why the inclusion criteria for non-TPO-RA studies were modified post-hoc?

A9: priority question

Page 109. Non-TPO-RA studies were included in further discussion and meta-analyses if they reported either platelet response, or time to response or duration of response. Why was bleeding rate not considered among the acceptable outcomes? Did any of the non-TPO-RA studies, which were excluded from further analyses, report bleeding rate?

A10:

Pages 102-103. Please clarify why relative risk is used for bleeding rates in Table B39 whilst odds ratio is used for response in Table B37 (and all other previous Tables)?

A11

Page 39. In the updated review, one study was excluded as the full text was not available. Please specify the reference for this study and what effort was made to obtain the full text publication from the authors or any other source?

A12

Page 58. Please clarify what is meant by a '*closed testing procedure'* in the context of logistic regression?

A13

Page 62-63 and 68-69. Please clarify how the number of patients who *"completed treatment"* in the CONSORT diagrams and the number of patients *"included in efficacy analysis"* have been derived (at present the numbers do not seem to add up). Similarly, please clarify which patients were included in the *"efficacy population"* and which in the *"ITT population" (pages 68-69).* Please clarify what is meant by *'Evaluable'* in Tables B16 and B18 and how these figures compare with those reported as *'completed treatment'* and *'included in efficacy analysis'* in the TRA 100773B CONSORT diagram?

A14

Page 69. Please clarify which column in Table B18 refers to eltrombopag and which to placebo?

A15

Pages 69 and 75. In the TRA 100773B and in the TRA102537 RAISE studies please clarify how blinding was maintained in case of significant bleeding or haemostatic challenge?

A16

Pages 84-85. There is a lack of information as to why some studies were excluded. Please clarify exclusion of studies according to the pre-specified inclusion criteria?

A17

Page 95. Please clarify whether figures in brackets represent range or IQR?

A18

Pages 97-98. Please clarify whether the graphs display percentages in each particular category?

A19

Page 104. The submission states that additional analyses are described in Section 7.10.4 but we could not find this section. Please clarify what is supposed to be contained in Section 7.10.4?

A20

Page 105. Please provide references for the 18 included non-TPO-RA randomised trials. Please also clarify why section 6.2.2 states that 18 RCTs were included, whereas Table B40 on page 106 lists 20 RCTs?

A21

Page 107. The submission states that 79 non-TPO-RA studies were subsequently excluded from further analyses due to their poor quality. Please clarify if the remaining included non-TPO-RA studies (Table B41) were considered robust quality, given about half of these studies were non-randomised and the quality of non-randomised evidence was not formally assessed in the submission?

A22

Page 132. Please clarify the exact inclusion status of the TRA 105325 EXTEND given that it is not very clear and it is difficult to track which results in subsequent Tables refer to TRA 105325 EXTEND?

A23

8.4.10 in the Appendices. Please clarify what “t” represents in the equation Mean= -t/In(0.5)?

A24

Did the three Eltrombopag RCTs recruit different patient populations or were the same patients included in more than one of the RCTs?

Section B: Clarification on cost-effectiveness data

B1: priority question

In order to enable the assessment of the evolution of patients through time, please provide information depicted in Table 1 (Appendix B) for the following (i.e ten tables of information),

a) Data from the RAISE trial from the eltrombopag arm and from the placebo arm for people splenectomised at baseline and non-splenectomised at baseline (four tables)

b) Data from the EXTEND trial, separately for those previously having received eltrombopag at entry to EXTEND and for those previously not having received eltrombopag at entry to EXTEND (i.e as if these ere two separate arms of the trial) for people splenectomised at baseline, and non-splenectomised at baseline (suitably adjusted for the timing of follow up assessments under the EXTEND trial) (four tables)

c) Data from the RAISE and EXTEND trials for eltrombopag responders, some of which underlies the responder patient analysis of figure B21. This should report the data collected under RAISE and EXTEND; i.e. including the extension data, for the RAISE eltrombopag responders as defined in Appendix 15. For people splenectomised at baseline, and non-splenectomised at baseline (two tables)

B2: priority question

There is no obvious link between the response rates in Table B36 and those reported for eltrombopag in either Table B19 or in Table B68. Please provide the inputs to the calculations of the eltrombopag response rates of table B68 (numerators and denominators). Similarly, please provide the parallel data from the placebo arm that would enable the parallel response rates for placebo to be calculated.

B3

In order to enable the assessment of the evolution of patients through time, please provide information depicted in table 1 (Appendix B) for the following(i.e 24 tables of information):

a) Data from the RAISE trial from the eltrombopag arm and from the placebo arm for people of Asian origin splenectomised at baseline, and of Asian origin non-splenectomised at baseline (four tables)

b) Data from the TRA100773A trial separately from the eltrombopag 50mg arm and from the placebo arm for people splenectomised at baseline, non-splenectomised at baseline, of Asian origin splenectomised at baseline, and of Asian origin non-splenectomised at baseline (including those discontinuing treatment due to high platelet response, suitably adjusted for the timing of follow up assessments under TRA100773A) (eight tables)

c) Data from the TRA100773B trial, separately from the eltrombopag arm and from the placebo for people splenectomised at baseline, non-splenectomised at baseline, of Asian origin splenectomised at baseline, and of Asian origin non-splenectomised at baseline (including those discontinuing treatment due to high platelet response, suitably adjusted for the timing of follow up assessments under TRA100773B) (eight tables)

d) Data from the Tomiyama 2009 trial, separately from the eltrombopag arm and the placebo arm, for people splenectomised at baseline, and non-splenectomised at baseline (suitably adjusted for the timing of follow up assessments under the Tomiyama 2009 trial). (four tables)

Section C: Clarification on quality of life data

C1: priority question

Please present overall goodness of fit estimates for the six models presented in Appendix 17.

C2: priority question

Please provide information depicted in Table 2 (Appendix C) for the observed SF-6D utilities and predicted SF-6D utilities from Model 6 of Appendix 17 of the submission, averaged across all the available data points.

C3

Within Appendix 17 please clarify whether the bleed variable was dichotomous or not and whether the severity of bleeds formed part of any analysis?

C4

Please clarify whether the WHO bleeding scale was considered as an explanatory variable within the utility analysis? If it was not explored, please provide a justification for this.

Section D: Clarification on resource use data

D1: priority question

Please split Table 30 in Appendix 15 by ELTR-ELTR and PLAC-ELTR patients. Please present the patient numbers underlying the resulting dosing figures**.**

D2: priority question

The average dose of eltrombopag is calculated using the RAISE study. The SPC for the drug specifies a lower starting dose for people of Asian origin. Please provide information depicted in Table 3 (Appendix D) for patients of Asian origin and non-Asian origin (two tables).

D3: priority question

Please provide information depicted in Table 3 (Appendix D), based on Table B37 page 101, for the subset of patients drawn from countries with a per capita income more than $2000 (one table).

D4

Please present the patient numbers underlying the dosing figures of Table 29 in Appendix 15.

D5

Please provide information depicted in Table 4 (Appendix D) for the Tomiyama 2009 trial, suitably adjusted for the timing of follow up assessments under the Tomiyama 2009 RCT for people of Asian origin and of non-Asian origin (two tables).

D6

Please clarify the countries and patient number (percentage) excluded from the RAISE data by the more than $2000 per capita criterion?

D7

Please clarify the countries and patient number (percentage) excluded from the EXTEND data by the more than $2000 per capita criterion.

Section E: Clarification on modelling and model validation

E1

The model schematic does not outline the possibility of rescue, and by implication failed rescue, but it does suggest that it is not possible to move directly from response to new treatment. This is also not immediately transparent from the excel cohort flow. Please clarify for a patient in the response state receiving rescue, where the rescue fails does the patient:

- remain in the response state?
- cease treatment and move to the LT NR state?
- have any probability of bypassing the LT NR state and moving immediately to a new treatment?

E2

Cell D141 of the Interim worksheet contains the probability of rescue and response for the LT NR state. Please clarify what is the modelling duration of this response, and how are these responders handled within the model?

E3

Please clarify what model inputs cells D28 and D32 of the Main worksheet change, and where these are in the the inputs' worksheet

E4

Within the IPD worksheet does the data in cells D6:D12 relate to the same definition of responder that underlies the responder analysis of figure B21? Does it also include all observations for these responders including observations made when the responder may have fallen below 50k, or does it relate to patient observations made when the patient had a contemporaneous platelet count of >50k?

Section F: Clarification on cost effectiveness estimates and model validation

F1: priority question

Section 6.8.1 mentions two validation reports. Please provide these.

F2: priority question

For the base case please tabulate the percentage of eltrombopag patients modelled for each cycle for the first six months of the model as:

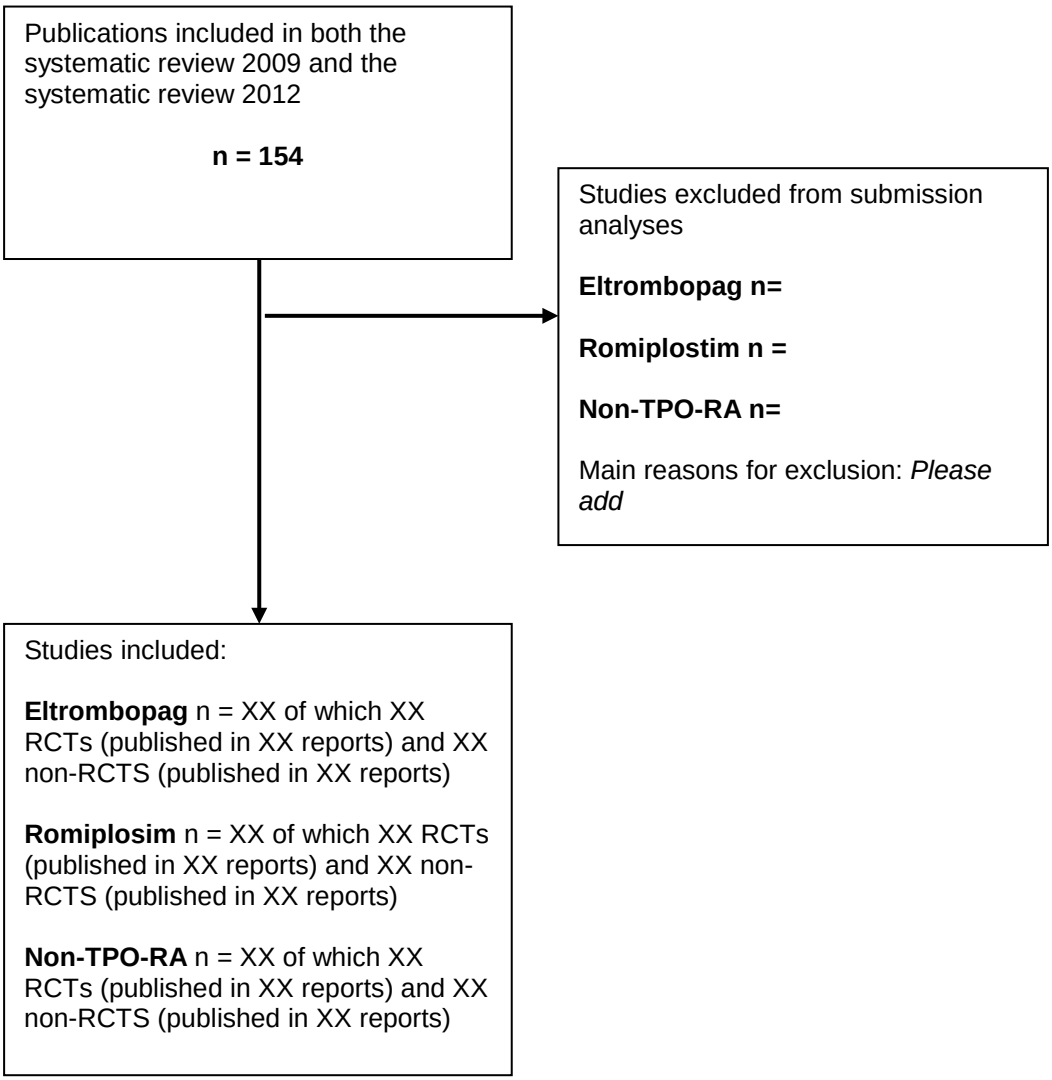
- Remaining alive and on eltrombopag, among those having had a response at any time point
- Remaining alive and on eltrombopag and being in response at that time point

- Remaining alive and on eltrombopag and not being in response at that time point
- Remaining alive and in the eltrombopag arm off treatment
- Receiving rescue therapy
- Having a minor bleed
- Having a major bleed
- Being hospitalised
- Discontinuing for reasons other than death
- Dying

Please cross tabulate these with number and percentage of patients in the RAISE eltrombopag arm in the same state and/or experiencing the relevant event.

Appendix A

Figure 1



Appendix B

Table 1

	Baseline	Day08	Day15	Day22	Day29	etc.
N on treatment	xxx	xxx	xxx	xxx	xxx	xxx
Of whom						
N 50k<= platelets	xxx	xxx	xxx	xxx	xxx	xxx
N 30k<= platelets <50k	xxx	xxx	xxx	xxx	xxx	xxx
N 15k<= platelets <30k	xxx	xxx	xxx	xxx	xxx	xxx
N platelets <15k	xxx	xxx	xxx	xxx	xxx	xxx
N discontinued	xxx	xxx	xxx	xxx	xxx	xxx
Reason for discontinuation						
N lack of efficacy	xxx	xxx	xxx	xxx	xxx	xxx
N loss of response if different from above	xxx	xxx	xxx	xxx	xxx	xxx
N AEs	xxx	xxx	xxx	xxx	xxx	xxx
N withdrawal of consent	xxx	xxx	xxx	xxx	xxx	xxx
N ....other reasons (please list)	xxx	xxx	xxx	xxx	xxx	xxx
N death	xxx	xxx	xxx	xxx	xxx	xxx

Appendix C

Table 2

Observed/predicted values		**All patients**	**Splenectomised**	**Non-Splenectomised**
Patients	Time points* (n observations)	Mean (s.e.)	Mean (s.e.)	Mean (s.e.)
RAISE all	Baseline	xxx	xxx	xxx
RAISE all	All RAISE excl baseline	xxx	xxx	xxx
RAISE all	All EXTEND	xxx	xxx	xxx
RAISE responders**	All RAISE when in response***	xxx	xxx	xxx
RAISE responders	All RAISE when not in response	xxx	xxx	xxx
RAISE responders	All EXTEND when in response	xxx	xxx	xxx
RAISE responders	All EXTEND when not in response	xxx	xxx	xxx
RAISE non-response	All RAISE excl baseline when not in response	xxx	xxx	xxx

* For example, for RAISE responders, the line referring to 'All RAISE when in response' would draw upon observed SF-6D values from the subgroup of RAISE responders, and for each responder only include the time points when that responder was actually in response. Please also report the number of observations within these time points.

**As per the definition of responders underlying Figure B21

***: i.e. 50k <= platelets at the relevant assessment time point

Appendix D

Table 3

	Indirect comparison eltrombopag versus. romiplostim (odds ratio, 95% CI)	
	Durable response	**Overall response**
All people	xxx	xxx
Splenectomised people	xxx	xxx
Non-splenectomised people	xxx	xxx

Table 4

	Splenectomised			**Non-splenectomised**		
Time period	N treated	Mean dose	S.E. dose	N treated	Mean dose	S.E. dose
Week 0-3	xxx	xxx	xxx	xxx	xxx	xxx
Week 4-7	xxx	xxx	xxx	xxx	xxx	xxx
Week 8-11	xxx	xxx	xxx	xxx	xxx	xxx
Week 12-15	xxx	xxx	xxx	xxx	xxx	xxx
Week 16-19	xxx	xxx	xxx	xxx	xxx	xxx
Week 20-23	xxx	xxx	xxx	xxx	xxx	xxx
Post-week 24	xxx	xxx	xxx	xxx	xxx	xxx