Eltrombopag for adult patients with chronic immune thrombocytopenic purpura (cITP)

GSK response to clarification questions – September 2012

Question	GSK response
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?	There are 37 non-TPO-RA studies included in the submission analysis. The final number of non-TPO-RA studies retrieved by the systematic reviews was 113 (not including studies reporting the outcome of a splenectomy). Please see Appendix A, Figure 1 for clarification. These are the final number of studies included in the submission. The 108 total and the 79 exclusions reported were errors and should have read 113 and 76 respectively.

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.	The inclusion criteria of the systematic reviews were broad and post-hoc criteria were used to select studies that were considered more relevant to the decision problem. We believe that UK patients are better represented by RAISE, TRA 773A and 773B than by all-Japanese studies. Furthermore these studies use different starting doses and a different dose schedule to those approved in the EU. Although these studies are not presented in the submission full data extraction was carried out for these studies and is available in the attached systematic reviews. At the time of the systematic search (February 2012), the Tomiyama study was only available as a conference abstract.
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?	Subjects who prematurely withdrew from TRA100773A and TRA100773B because of platelet counts >200Gi/L, had their last platelet count whilst on treatment used in the analysis at Day 43. Subjects who withdrew prematurely for any other reason were considered non-responders, regardless of the platelet count. For RAISE, patients who withdrew early from the study were classified as non responders from the time of withdrawal and for all subsequent nominal visits as used in the analysis. Patient numbers used in the meta-analysis correspond to the patient numbers used to derive the odds ratio for response in each trial.

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.

The sustained response for eltrombopag is not comparable to the overall response for romiplostim.

Durable response was the primary end point for the romiplostim studies with overall response being reported as a secondary outcome. Durable response was defined in the romiplostim trials based on platelet counts being assessed on a weekly basis. Neither durable nor overall response were pre-specified end points for the RAISE trial and after 6 weeks patients did not have to be assessed on a weekly basis. However, a post-hoc analysis of sustained and overall response for the RAISE trial was available.

Sustained response for eltrombopag was compared to durable response for romiplostim through an indirect treatment comparison. Overall response for eltrombopag and romiplostim was also compared via an indirect treatment comparison.

Differences in definitions (see table below), study design and the prespecified versus post-hoc nature of these analyses (as discussed on page 99-100 of the submission) mean that whilst it was considered appropriate to conduct an indirect comparison, these differences should be taken into account when interpreting the results.

	Response definitions	
	Eltrombopag	**Romiplostim**
Analysis type	Post-hoc analysis.	Pre-specified analysis
Study design differences	After the initial 6 weeks of the trial, patients with a stable platelet count could be assessed monthly. To simulate weekly platelet assessments this post hoc analysis of RAISE makes the assumption that patients remain at the same platelet level from one assessment to the next. Reductions in concomitant medications were allowed at any time after the first 6 weeks of the study. Investigators were encouraged to reduce concomitant medications once a stable dose/platelet count was achieved.	Analysis based on weekly assessments. Reductions in concomitant medications were only allowed in the first 12 weeks of the studies.

Definitions	Eltrombopag	Romiplostim
	Sustained response	**Durable response**
	Platelet count elevation ≥50 and ≤400 x 10^9/L for at least 6 of the last 8 weeks of treatment. Patients taking rescue medication at any time were not considered to have achieved a sustained response. Patients who withdrew early were considered not to have achieved a sustained response.	Weekly platelet responses (platelet counts ≥ $50x10^9$/L) during 6 or more weeks of the last 8 weeks of treatment. Patients who received rescue medications at any point during the study could not be counted as having a durable response
	Overall response	**Overall response**
	Patients with either a sustained or transient response. Transient response defined as platelet count elevation ≥50 and **≤400** x 10^9/L for at least 4 **consecutive** weeks during treatment and included all data up to time of withdrawal. Platelet count elevations during periods of rescue treatment and up to the time platelet counts fell below $50x10^9$/L after the end of the rescue medication period, were not considered responses.	Durable plus transient rates of platelet response. Transient response defined as 4 or more weekly responses (platelet counts ≥ $50x10^9$/L), without a durable response from week 2 – 25 of therapy. Platelet responses that occurred within 8 weeks after receiving rescue medications were not considered responses.

Not all subjects in the RAISE study completed 6 months of treatment, the numbers were presented both for the subjects who received 6 months or more of treatment and for the ITT population (which comprised all randomised subjects)

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?	With regard to bleeding data the number of total bleeds experienced could not reliably be estimated from a 43 day study. As a result of the short trial durations, the low number of clinically significant bleeds (WHO 2-4) in the TRA100773A/B studies would mean that synthesising the data would have added little value. With regard to SF-36 data, although it is reasonable to expect that platelet elevation would be observed by 43 days, it seems less likely that the impact on patient quality of life would be realised within this period.
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?	Although the dose appears to level out at 6 weeks, the relative treatment effects over the first 6 weeks cannot be considered representative of long term efficacy. An indirect comparison versus romiplostim was enabled by the availability of a post-hoc analysis of sustained and overall response for the RAISE study which could be considered similar to the data available for the romiplostim studies. As TRA100773A/B were only 6 week studies a similar analysis of sustained and overall response was not possible. This would require at least 8 weeks of data (sustained response is defined as 6 platelet responses in the last 8 weeks of treatment). Due to the small number of clinically significant bleeds, the inclusion of the TRA100773A/B studies in the indirect comparisons of bleeding would have added little value to the analysis.

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'.

'3.14' in Table B37 (reproduced below) is correct.

Indirect comparison of platelet response rates

	Indirect comparison eltrombopag versus. romiplostim (odds ratio, 95% CI)	
	Durable response	**Overall response**
All subjects	0.32 (0.03, 3.14)	0.22 (0.05, 1.02)
Splenectomised subjects	0.50 (0.01, 17.32)	0.09 (0.00, 2.52)*
Non-splenectomised subjects	0.41 (0.04, 4.80)	0.34 (0.06, 2.14)

* This result varies from that in the public domain as an inconsistency in the handling of zero events was identified and has been corrected

Zero events have been handled by applying 0.5 to all values for that trial. Zero events are only present in the romiplostim data (splenectomised patients, placebo arm). For the indirect comparison of overall response in splenectomised patients 0.5 had incorrectly been added to both the eltrombopag and romiplostim data. This was inconsistent with how zero events were handled for overall response in splenectomised patients where 0.5 had only been added to the romiplostim data. This correction changed the odds ratio for durable response of eltrombopag versus romiplostim in splenectomised patients from 0.08 (0.00,1.93) to 0.09 (0.00,2.52).

A8: priority question Page 107. Please clarify if and why the inclusion criteria for non-TPO-RA studies were modified post-hoc?	The inclusion criteria of the systematic reviews were broad and included studies in patients with primary ITP where at least some patients had platelet counts <30 X109/L. The review returned a large number of studies in patients with clearly less severe and refractory disease than those under consideration in this appraisal. In particular many studies included patients with short disease duration, higher platelet levels and/or who were treatment naïve. In addition, variation in the definition of platelet response also made it difficult to compare study results. Post-hoc criteria were used to select studies that were more relevant to the decision problem and which provided comparable outcome data. These studies are presented in the submission and included in the naive indirect comparison. Full data extraction was however carried out on all non-TPO-RA papers and is available in the attached systematic reviews.
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?	The systematic review retrieved 15 studies reporting bleeding endpoints (not including the studies of the splenectomy procedure or the eltrombopag or romiplostim studies). Only five of the 37 non-TPO-RA studies included in the submission reported bleeding endpoints. Considerable variation was seen in the nature of the bleed endpoints reported and in many cases the exact meaning of the endpoints reported was unclear (e.g. “Relative to day 7, bleeding worsened in 16 patients (14%) by day 21” or “Regression of haemorrhages, defined as the absence of any important spontaneous bleeding during the first 10 or 14 days”). For these reasons comparison or synthesis of this data within the submission was not deemed to be feasible. Reporting of platelet response was far more comprehensive and the correlation between low platelet counts and bleed rates is well established (see submission references). Bleeding endpoint data was extracted for all non-TPO-RA studies as part of the systematic review.

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)?

Odds ratios for bleeding rates are provided below. As for the comparison of the relative risk of bleeding, the use of odds ratios also demonstrates that there is no significant difference in clinically significantly bleeding between eltrombopag and romiplostim.

Grade 3-5 bleeding events; odds ratios	**Eltrombopag vs placebo OR (95% CI)**	**Romiplostim vs placebo OR (95% CI)**	**Indirect comparison eltrombopag vs. romiplostim OR (95% CI)**
All subjects	0.33 (0.07, 1.52)	0.55 (0.16, 1.94)	0.60 (0.08, 4.29)
Splenectomised subjects	0.08 (0.00, 1.68)	0.45 (0.10, 2.00)	0.17 (0.01, 5.31)
Non-splenectomised subjects	0.71 (0.12, 4.45)	0.95 (0.08, 11.14)	0.75 (0.03, 16.13)
Grade 2-5 bleeding events; odds ratios	**Eltrombopag vs placebo OR (95% CI)**	**Romiplostim vs placebo OR (95% CI)**	**Indirect comparison eltrombopag vs. romiplostim OR (95% CI)**
All subjects	0.57 (0.23, 1.45)	0.35 (0.15, 0.85)	1.63 (0.46, 5.80)
Splenectomised subjects	0.37 (0.08, 1.65)	0.44 (0.14, 1.40)	0.83 (0.13, 5.49)
Non-splenectomised subjects	0.75 (0.23, 2.45)	0.25 (0.06, 1.00)	3.05 (0.48, 19.15)

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?

Chong BH, Gan E, Bird R, Pidcock M, Lloyd J, Tay L, et al. An open-label, multicenter study evaluating the efficacy and safety of a new 10% liquid intravenous immunoglobulin in patients with primary immune thrombocytopenia (ITP). Asia-Pacific Journal of Oncology and Hematology 2010; 2(2).

The full paper of this citation was not available. The British Library did not stock the publication and our US source (Washington Document Delivery) was unable to get hold of the paper after contacting all of their back up sources.

We did not contact the authors of this publication.

A12 Page 58. Please clarify what is meant by a '*closed testing procedure'* in the context of logistic regression?	Section 11.3.1 of the protocol provides details of planned interim analyses for the study including the closed testing procedures used to test for efficacy and futility, details of the critical boundaries and how they were derived are also given. The global null hypothesis of no treatment difference between the four treatment groups in the study (placebo, eltrombopag 30mg, 50mg, 75mg) was first tested using a logistic regression model. Upon rejection of this global null hypothesis, a pre-defined order of testing to assess efficacy and futility of each dose of eltrombopag vs placebo was followed.
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?	Pages 62-63: The numbers who 'completed treatment' are calculated as the difference between the number of subjects who took at least one dose of study medication and those who prematurely withdrew from the study. The numbers included in the efficacy analysis are those subjects who were in the efficacy population (see Page 58: The efficacy population was the primary population for efficacy analyses and comprised all randomised subjects treated with ≥ 1 dose of study medication, who had a baseline platelet count of < $30X10^9$/L). Subjects were usually excluded from the efficacy population either due to their baseline platelet count being missing or >30Gi/L. Pages 68-69: The Intent-to-Treat population comprised of all patients randomized who received at least one dose of study medication and with at least one platelet count post-dosing. The efficacy population was defined as above. Figure B16: The number of evaluable patients refers to the number of subjects in the efficacy population who either had a platelet count at Day 43 or who were identified to be an early withdrawal. There were 2 subjects in TRA100773B (1 in placebo and 1 in eltrombopag) with no platelet count information at Day 43 and no indication that they were prematurely withdrawn. These 2 subjects were not considered to be evaluable for response.

<table>
<tr><td></td><td>Figure B18: The number of evaluable patients in the first part of the table refers to the number of subjects in the efficacy population with a WHO bleeding assessment at Day 43. The number of evaluable patients in the second part of the table refers to the number of subjects in the ITT population.</td></tr>
<tr><td>A14

Page 69. Please clarify which column in Table B18 refers to eltrombopag and which to placebo?</td><td>Table B18 should be labelled as follows:

<table>
<tr><th></th><th>Eltrombopag</th><th>Placebo</th></tr>
<tr><td>WHO G1-4 bleeding, day 43</td><td colspan="2">Efficacy population</td></tr>
<tr><td>Evaluable, n</td><td>51</td><td>30</td></tr>
<tr><td>Patients experiencing bleeding, n (%)</td><td>20 (39)</td><td>18 (60)</td></tr>
<tr><td>OR</td><td></td><td>0.27</td></tr>
<tr><td>95% CI</td><td></td><td>0.09,0.88</td></tr>
<tr><td>p-value (two sided)</td><td></td><td>0.029</td></tr>
<tr><td>WHO G1-4 bleeding, any point during treatment</td><td colspan="2">ITT population</td></tr>
<tr><td>Evaluable, n</td><td>76
8</td><td>3</td></tr>
<tr><td>Patients experiencing bleeding, n (%)</td><td>46 (61)</td><td>30 (79)</td></tr>
<tr><td>OR</td><td></td><td>0.49</td></tr>
<tr><td>95% CI</td><td></td><td>0.26,0.89</td></tr>
<tr><td>p-value (two sided)</td><td></td><td>0.021</td></tr>
</table>
</td></tr>
<tr><td>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?</td><td>A significant bleeding event or haemostatic challenge on its own would not constitute a reason for un-blinding because investigators were allowed to use rescue medication at any time they deemed necessary. Therefore regardless of the ‘response status’ or treatment group of the patient, the decision to use rescue was made based on the platelet count and the clinical situation and did not require un-blinding.</td></tr>
</table>

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?	None of these studies were excluded from further consideration due to the pre-specified inclusion criteria. They were each excluded due to their limited relevance to the decision problem. The reasons are documented in the tables on pages 84-85.
A17 Page 95. Please clarify whether figures in brackets represent range or IQR?	Data presented in brackets represents the range with the exception of the baseline platelet counts for the total population where an IQR has been provided. The corresponding ranges (min-max) would be (2-87) for placebo and (0-78) for eltrombopag.
A18 Pages 97-98. Please clarify whether the graphs display percentages in each particular category?	This is correct. 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?	This refers to section 6.10.4.
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?	This is an error in section 6.2.2, the 20 studies listed in Table B40 is the correct number of RCTs. The references for 19 out of the 20 have been provided with the initial submission. We have been unable to source the Mazzucconi 1985 paper.

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?	This referred to the quality of reporting in the studies. Both endpoint data and key characteristics of the patient population (e.g. whether patients had received prior treatment) were often not reported. This along with a large number of studies being in less severe or refractory populations (see response A8) explains the high number of exclusions. The comment did not relate to study quality. As stated within the submissions there are concerns regarding much of the non-TPO-RA evidence base.
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?	EXTEND met the inclusion criteria. In addition to the details regarding methods provided in Table B52 results are presented in Table B53 in the row labelled “TRA 105325 EXTEND, Saleh and Bussel 2011 ASH (abs no. 3296 and 3297)44-46;129” (page 135-136).
A23 8.4.10 in the Appendices. Please clarify what “t” represents in the equation Mean= -t/In(0.5)?	t = median time
A24 Did the three Eltrombopag RCTs recruit different patient populations or were the same patients included in more than one of the RCTs?	For each of the TRA 100773A, B and RAISE: patients were excluded if they had previously participated in any study containing eltrombopag, i.e. the studies recruited different patient populations.

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	Tables for B1a and b have been provided alongside this document. Tables for B1c will be provided by September 21st 2012.

<table>
<tr><td>splenectomised at baseline, and non-splenectomised at baseline (two tables)</td><td></td></tr>
<tr><td>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.</td><td>Table B36 presents a post-hoc analysis of sustained (durable) response and overall response for the RAISE trial. The definitions of response used here enabled an indirect comparison with the response outcomes reported in the Kuter 2008 studies as documented throughout the submission.

The data presented in Table B19 and Table B68 represent the proportions of patients experiencing a response at any point in the study. For these analyses response is defined as per the RAISE primary endpoint.

The difference between Table B19 and Table B68 is that table B19 described the overall population whereas Table B68 stratifies response according to splenectomy status. The data requested are provided below.

<table>
<tr><th>Patient group</th><th>Responders</th><th>N</th></tr>
<tr><td>Eltrombopag – splenectomised</td><td>38</td><td>50</td></tr>
<tr><td>Eltrombopag – non-splenectomised</td><td>68</td><td>85</td></tr>
<tr><td>Placebo – splenectomised</td><td>4</td><td>21</td></tr>
<tr><td>Placebo – non-splenectomised</td><td>13</td><td>41</td></tr>
</table>
</td></tr>
</table>

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	Tables for B3a are provided alongside these responses. Tables for B3b and c will be sent to NICE by 21st September 2012. We are currently liaising with our colleagues in Japan to provide tables for B3d however we cannot guarantee that these will be available by the 21st September 2012.

<table>
<tr>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>C1: priority question

Please present overall goodness of fit estimates for the six models presented in Appendix 17.</td>
<td>The number of covariates and the -2 log likelihood statistics are provided in the table below.

<table>
<tr><th>Model</th><th>Number of Covariates</th><th>-2 Log Likelihood</th></tr>
<tr><td>Model 1: Repeated-measures model with all variables, Full Model</td><td>5</td><td>3167.0</td></tr>
<tr><td>Model 2: Repeated-measures model, Full Model - [Splenectomy at Baseline]</td><td>4</td><td>3166.7</td></tr>
<tr><td>Model 3: Repeated-measures model, Full Model - [Time from Baseline Utility]</td><td>4</td><td>3165.9</td></tr>
<tr><td>Model 4: Repeated-measures model, Full Model - [Time from Baseline Utility] - [Logit of Baseline Utility]</td><td>3</td><td>3267.7</td></tr>
<tr><td>Model 5: Repeated-measures model, Full Model - [Time from Baseline Utility] + [Platelet*Bleed Interaction]</td><td>5</td><td>3168.4</td></tr>
<tr><td>Model 6: Repeated-measures model, Full Model - [Time from Baseline Utility] + [Splenectomy*Bleed Interaction]</td><td>4</td><td>3162.3</td></tr>
</table>
</td>
</tr>
</table>

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.	Please see appendix B.
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?	Yes the bleed variable was dichotomous. The severity of bleeding according to the ITP Bleeding Score was used to determine whether or not the bleed was included in the analysis. This was done to identically match the categorisation of bleeds as 'daycase' in the analyses of bleed rates (see p89 of appendices document). These rates drive the incidence of the utility decrement within the cost-effectiveness model.
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.	No, the ITP Bleeding Score was chosen over the WHO Bleeding Scale for all the economic analyses (i.e. bleed rates and utility conditional upon bleed occurrence). The ITP Bleeding Score provides detailed information regarding bleed type, which is not available from the four level WHO Bleeding Score. This made it easier to determine whether the bleeds would have required daycase hospitalisation.
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**.**	Please see appendix C.

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).	We believe that an indirect comparison of durable and overall response in Asian and non-Asian patients would not be appropriate as these disaggregated data are not available for the romiplostim studies. Furthermore as discussed in the submission the indirect comparison of durable and overall response is associated with significant uncertainty as a result of small patient numbers and differences in response definitions and study design. A sub group analysis of RAISE would result in further uncertainty and we believe would not inform the decision problem.
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).	As stated in our response to D2, GSK do not feel that it would be appropriate to conduct an indirect comparison using a subgroup of the RAISE trial as this would increase the uncertainty in the analysis and would not inform the decision problem. Disaggregated data is also not available for the romiplostim studies. The purpose of looking at data from countries with a per capita income greater or less than $2000 was to take into account differences in the provision of expensive concomitant/rescue treatments. There is no reason to believe that efficacy of eltrombopag would be different in these two groups.
D4 Please present the patient numbers underlying the dosing figures of Table 29 in Appendix 15.	Please see table 3 in appendix C.
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).	This trial was only conducted in the Japanese population. All subjects were considered to be of Asian origin.

D6

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

Total number of patients (all countries) = 197.
Percentage of patients in countries less than $2,000 per capita = 96/197 = 48.7%.
The proportion accounted for by each country within this group is presented in the table below.

RAISE

Countries less than $2,000 per capita	N (%)
China	12 (12.5)
Czech Republic	6 (6.3)
Hong Kong	12 (12.5)
Peru	13 (13.5)
Poland	15 (15.6)
Russian Federati	11 (11.5)
Slovakia	3 (3.1)
Taiwan	5 (5.2)
Tunisia	6 (6.3)
Ukraine	9 (9.4)
Vietnam	4 (4.2)
Total <$2,000 per capita	96 (100)

D7

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

Total number of patients (all countries) = 145
Percentage of patients in countries less than $2,000 per capita = 72/145 = 49.7%.
The proportion accounted for by each country within this group is presented in the table below.

EXTEND

Countries less than $2,000 per capita	N (%)
China	10 (13.9)
Czech Republic	6 (8.3)
Hong Kong	10 (13.9)
Peru	8 (11.1)
Poland	10 (13.9)
Russian Federati	10 (13.9)
Slovakia	2 (2.8)
Taiwan	2 (2.8)
Tunisia	4 (5.6)
Ukraine	7 (9.7)
Vietnam	3 (4.2)
Total <$2,000 per capita	72 (100)

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?	From a structural perspective patients receiving rescue remain in the response state regardless of the outcome of rescue treatment. However in the base case patients in a response state have zero risk of receiving rescue treatments.
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?	Response to rescue is assumed to last for one model cycle (1 month). Responders are assumed to remain in the LT NR state in the following cycle. For the cycle in which they respond they experience the higher utility and lower bleed rates associated with an elevated platelet level (>50k).

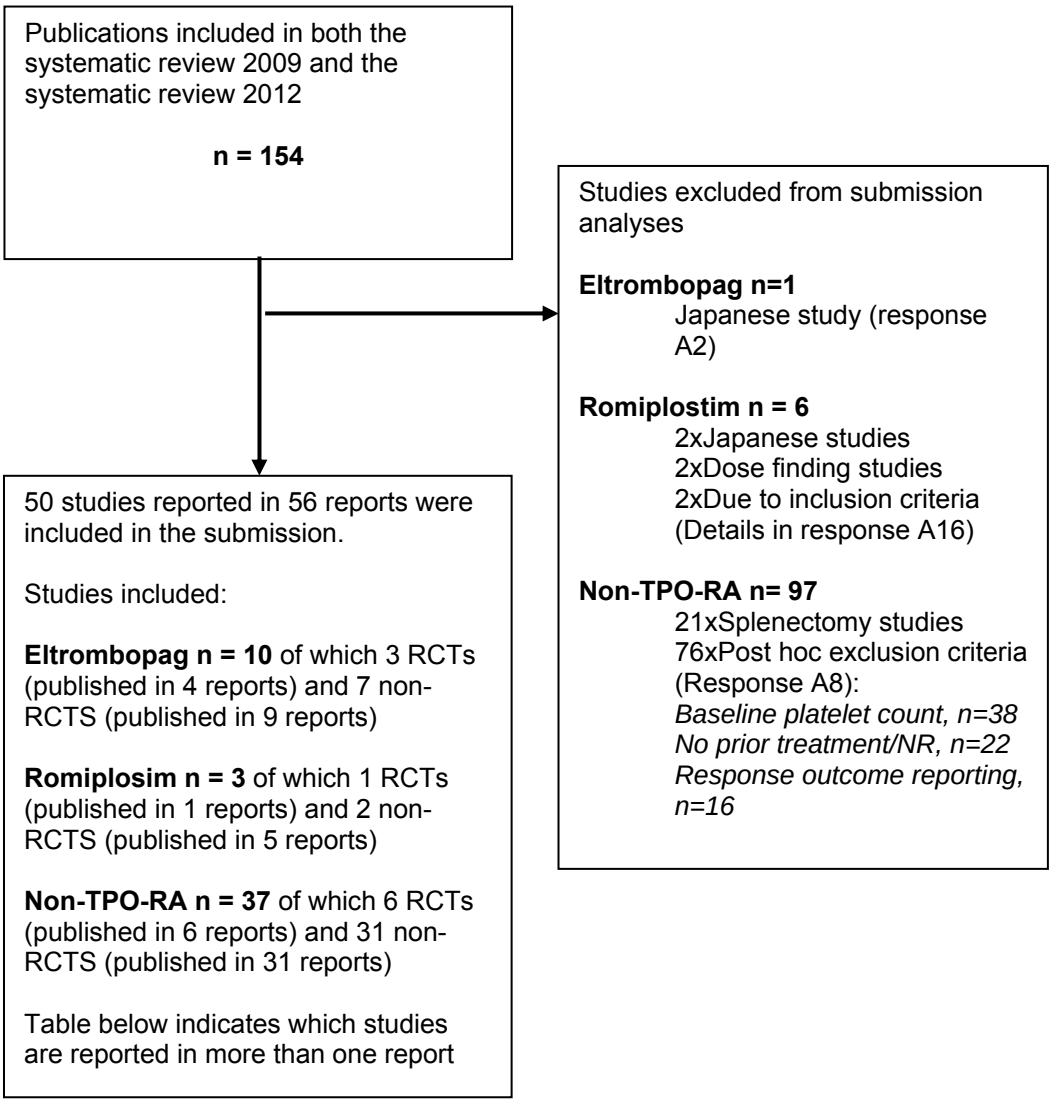
E3 Please clarify what model inputs cells D28 and D32 of the Main worksheet change, and where these are in the the inputs' worksheet	D28 allows the user to change the data relating platelet level to long term outcomes from TA221 (the base case) to data taken from the eltrombopag trial program. Switching between the base case and use of data from the eltrombopag trial program alters the following: 1) Response rate of non-TPO-RA treatment taken from systematic review (Transition probabilities C74:C89) 2) Time on treatment of non-TPO-RA treatments taken from systematic review (Transition probabilities D169:D178) 3) Total rate of rescue conditional upon platelet level taken from RAISE/EXTEND (Transition probabilities D195:D196) 4) Proportions of patients receiving each rescue from RAISE/EXTEND (Drugs costs C87:C90) 5) Probabilities of bleed conditional upon platelet level from RAISE/EXTEND (Transition probabilities E22:E25) Further detail regarding this scenario is provided in section 6.3.1 under the headings with suffix "Alternative evaluation". D32 allows the user to run an analysis that more closely approximates the assumptions used in TA221. This makes the following changes from the base case: 1) Average romiplostim vials used taken from TA221 (Vial wastage calculations C11:I11) 2) TPO-RA response rate switched to TA221 rate (Transition probabilities C57) 3) Rescue rates inflated to reflect TA221 values (Interim D128) 4) Proportion of patients receiving rituximab switched to TA221 value and sequence altered to include rituximab (Transition probabilities D7; see also macro within "Main" sheet for sequence change) 5) Health state utilities switched to TA221 values (Utilities AEs C6:C13) 6) Time on TPO treatment switched to TA221 value (Interim D88; Markov C23:C712)

	7) Follow-up cost per month switched to TA221 value (Other Costs C30) and percent of patients receiving home administration switched to 100% (Drug costs D73:D81) Further detail regarding this scenario is provided in section 6.6.2 of the submission in the section entitled “multi-way sensitivity analyses”.
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?	No the data in figure B21 describes time on treatment for patients who achieve the RAISE definition of response at least once during RAISE follow-up. The data in the IPD worksheet describes event rates according to the platelet level the patient had at the time of the event (i.e. when they had a contemporaneous platelet count of >=50k). This analysis includes data from patients allocated to both placebo and eltrombopag in RAISE and from patients receiving eltrombopag in EXTEND. The process for obtaining these counts is described in Appendix 15.
F1: priority question Section 6.8.1 mentions two validation reports. Please provide these.	These have been provided alongside our responses. Please note that these reports were based on an early version of the economic model, marginally different to the one submitted to NICE. The main differences between the submitted model and that which was validated are: • Corrections to time on treatment analysis incorporated in submitted version • Eltrombopag and romiplostim AEs rates set equal • Some small programming errors were identified and corrected (e.g. half cycle correction removed for non-TPO admin and acquisition costs). None of these changes had a substantive impact on the results of the model. Subsequently, we have identified a small error in the model that was submitted to NICE. The nature of this error and how to correct it are detailed in appendix E. Correction of this error does not significantly impact model results.

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.	The derivation of these values and the values themselves are presented in appendix D in this document. Note that we have not provided data on total hospitalisations as this was not collected in RAISE.

Appendix A

Figure 1



	Study	References
Eltrombopag	RAISE, n=2 (RCT)	Cheng 2008, Cheng 2010
	EXTEND, n=3 (non-RCT)	Saleh ASH 2010, Saleh ASH 2011, Bussel EHA 2009
Romiplostim	Bussel 2009, n=3 (non-RCT)	Bussel 2009, Bussel ASH 2009, Kuter ASH 2010
	Janssens, n=2 (non-RCT)	Janssens ASH 2011, Janssens EHA 2011

Appendix B

Table 1

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 (n=187)	Obs=.715(.696,.734) Prd=.748(.732,.764)	Obs=.696(.665,.726) Prd=.721(.691,.749)	Obs=.726(.702,.751) Prd=.764(.743,.783)
RAISE all	All RAISE excl baseline (n=509)	Obs=.716(.704,.728) Prd=.748(.732,.763)	Obs=.703(.684,.722) Prd=.732(.704,.758)	Obs=.724(.709,.739) Prd=.757(.737,.776)
RAISE all	All EXTEND (n=1300)	Obs=.722(.714,.729) Prd=.749(.727,.769)	Obs=.708(.695,.721) Prd=.730(.690,.766)	Obs=.730(.720,.740) Prd=.759(.733,.784)
RAISE responders**	All RAISE when in response*** (n=242)	Obs=.739(.721,.757) Prd=.764(.737,.790)	Obs=.711(.678,.743) Prd=.728(.674,.776)	Obs=.752(.731,.773) Prd=.784(.752,.813)
RAISE responders**	All RAISE when not in response*** (n=99)	Obs=.715(.690,.740) Prd=.735(.710,.759)	Obs=.704(.662,.746) Prd=.725(.682,.763)	Obs=.722(.690,.754) Prd=.741(.710,.770)
RAISE responders**	All EXTEND when in response*** (n=632)	Obs=.744(.732,.755) Prd=.772(.741,.799)	Obs=.710(.689,.730) Prd=.747(.686,.799)	Obs=.758(.745,.772) Prd=.785(.751,.816)
RAISE responders**	All EXTEND when not in response*** (n=233)	Obs=.712(.694,.731) Prd=.753(.723,.780)	Obs=.722(.691,.753) Prd=.724(.667,.774)	Obs=.707(.684,.731) Prd=.769(.734,.800)
RAISE non-response**	All RAISE excl baseline when not in response*** (n=167)	Obs=.685(.665,.704) Prd=.726(.698,.751)	Obs=.696(.666,.726) Prd=.734(.693,.771)	Obs=.675(.648,.703) Prd=.721(.684,.755)

* Since the dependent variable of Model 6 was the logit transformation of SF-6D, standard errors for predicted values of non-transformed SF-6D are not estimable; therefore, 95% confidence intervals are presented for all observed and predicted estimates.

**As per the definition of responders underlying Figure B21

*** being 'in response' implies platelets >=50k at the relevant assessment time point

Appendix C

Table 1: Eltrombopag dose (RAISE Placebo, EXTEND - Eltrombopag)

Splenectomised status	N	Mean	SE
Non-splenectomised status	33	48.28	0.158
Splenectomised status	14	52.66	0.249
All	47	49.4	0.134

Table 2: Eltrombopag dose (RAISE Eltrombopag, EXTEND - Eltrombopag)

Splenectomised status	N	Mean	SE
Non-splenectomised status	62	49.88	0.116
Splenectomised status	36	52.62	0.166
All	98	50.79	0.095

Table 7: Mean dose over time in RAISE (SE)

Week	Non-splenectomised	N*	Splenectomised	N*
0-3	48.51 (0.873)	85	48.96 (1.244)	50
4-7	54.62 (2.024)	81	56.81 (2.952)	49
8-11	55.49 (2.195)	78	57.78 (3.114)	48
12-15	55.12 (2.395)	78	56.871 (3.2)	46
16-19	56.20 (2.210)	76	54.66 (3.38)	45
20-23	57.13 (2.219)	74	57.35 (3.225)	44

* Count includes patients that recorded at least one dose at any point in the four week interval.

Appendix D

Data	Model estimation	RAISE data estimation*
1. Alive on eltrombopag and have had a response at any time point	Patients in eltrombopag "LT Resp" state at end of each cycle (cycle 0 is the proportion of responders at any time point).	Kaplan Meier data for time on treatment for responders (at any time point) is multiplied by the proportion of patients achieving a response (at any time point).
2. Alive on eltrombopag (in response)	As per (1). Patients are assumed to maintain their response.	Kaplan Meier data for time on treatment for all patients is multiplied by the following for a given month (*t*): (patients with RAISE response at nearest assessment prior to *t)*/(patients with time on treatment>=*t)*
3. Alive on eltrombopag (not in response)	All patients who respond at any time point are assumed to maintain this response whilst on treatment. No patients are therefore assumed to be on treatment and not in response beyond the initial time to response period.	Kaplan Meier data for time on treatment for all patients is multiplied by the following for a given month (*t*): (patients without RAISE response at nearest assessment prior to *t)*/(patients with time on treatment>=*t)*
4. Alive off eltrombopag treatment	Cumulative proportion alive off eltrombopag	1 – Kaplan Meier data for time on treatment for all patients
5. Rescue events	Per cycle rate of rescue (all rescue types)	Total number of rescue events in month (Anti-D; IVIg; IV steroids; platelet transfusions) divided by number of patients
6. Minor bleed	Per cycle rate of outpatient bleeds	Total number of rescue events in month (Anti-D; IVIg; IV steroids; platelet transfusions) divided by number of patients
7. Major bleed	Per cycle rate of inpatient bleeds	Total number of outpatient bleeds in month divided by number of patients
8. Discontinued for reasons other than death	Cumulative proportion of patients discontinuing for reasons other than death at end of cycle	Total number of inpatient bleeds in month divided by number of patients
9. Dead	Cumulative proportion of patients dead at end of cycle	No patients in the eltrombopag arm of RAISE died during the trial.

* Patients included in this analysis are patients randomised to eltrombopag in RAISE. Calculations for splenectomised and non-splenectomised patients are performed separately.

Splenectomised

Model

Month	Alive on eltrombopag and have had a response at any time point	Alive on eltrombopag (in response)	Alive on eltrombopag (not in response)	Alive off eltrombopag treatment	Rescue events [in that cycle]	Minor bleed [in that cycle]	Major bleed [in that cycle]	Discontinued for reasons other than death	Dead
0	76%	0%	100%	0%	0.42	0.20	0.01	0%	0%
1	76%	76%	0%	24%	0.17	0.12	0.01	24%	0%
2	74%	74%	0%	26%	0.18	0.13	0.01	26%	0%
3	72%	72%	0%	27%	0.19	0.13	0.01	27%	0%
4	71%	71%	0%	29%	0.20	0.13	0.01	29%	0%
5	69%	69%	0%	31%	0.19	0.13	0.01	31%	0%
6	67%	67%	0%	33%	0.18	0.13	0.01	33%	0%

Clinical trial data

Month	Alive on eltrombopag and have had a response at any time point	Alive on eltrombopag (in response)	Alive on eltrombopag (not in response)	Alive off eltrombopag treatment	Rescue events [in that cycle]*	Minor bleed [in that cycle]	Major bleed [in that cycle]	Discontinued for reasons other than death	Dead
1	76%	42%	56%	2%	0.097 / 0.080	0.460	0.000	2%	0%
2	72%	44%	50%	6%	0.032 / 0.020	0.160	0.000	6%	0%
3	70%	44%	48%	8%	0.129 / 0.080	0.120	0.000	8%	0%
4	68%	42%	46%	12%	0.194 / 0.120	0.120	0.000	12%	0%
5	64%	42%	42%	16%	0.129 / 0.080	0.080	0.000	16%	0%
6	64%	47%	37%	16%	0.194 / 0.120	0.100	0.000	16%	0%

* High health care expenditure / all

Non-splenectomised

Month	Alive on eltrombopag and have had a response at any time point	Alive on eltrombopag (in response)	Alive on eltrombopag (not in response)	Alive off eltrombopag treatment	Rescue events [in that cycle]	Minor bleed [in that cycle]	Major bleed [in that cycle]	Discontinued for reasons other than death	Dead
0	80%	0%	100%	0%	0.20	0.25	0.02	0%	0%
1	80%	80%	0%	20%	0.07	0.13	0.01	20%	0%
2	79%	79%	0%	21%	0.07	0.13	0.01	21%	0%
3	78%	78%	0%	21%	0.07	0.13	0.01	22%	0%
4	77%	77%	0%	22%	0.07	0.14	0.01	23%	0%
5	76%	76%	0%	23%	0.07	0.13	0.01	24%	0%
6	75%	75%	0%	24%	0.06	0.13	0.01	25%	0%

Month	Alive on eltrombopag and have had a response at any time point	Alive on eltrombopag (in response)	Alive on eltrombopag (not in response)	Alive off eltrombopag treatment	Rescue events [in that cycle]*	Minor bleed [in that cycle]	Major bleed [in that cycle]	Discontinued for reasons other than death	Dead
1	79%	53%	42%	5%	0.081 / 0.047	0.376	0.000	5%	0%
2	79%	62%	29%	8%	0.324 / 0.153	0.106	0.012	8%	0%
3	79%	61%	29%	10%	0.405 / 0.200	0.106	0.012	10%	0%
4	78%	53%	35%	12%	0.135 / 0.059	0.035	0.012	12%	0%
5	76%	52%	35%	13%	0.000 / 0.000	0.047	0.000	13%	0%
6	75%	57%	27%	17%	0.027 / 0.012	0.047	0.000	17%	0%

* High health care expenditure / all

Appendix E

The nature of the error identified and how to rectify this in the economic model is outlined below. Correction of this error does not substantively impact on results.

The risk of inpatient bleeds should double in the final NR state. However in the utility calculations in the model, the risk of both inpatient and outpatient bleeds is doubled [corrected by deleting the green section of the formulae below], and the half cycle correction for this component of the calculation is absent [corrected by inserting the yellow text]. In addition in some instances the utility implications of inpatient bleeds are incorrect [corrected by modifying the red values].

The following change is required to correct this in the model sent to NICE. The formulae in the Markov worksheet cell CO23 should be changed to the following (alterations highlighted). This should then be dragged down to CO712.

=(SUM(Q23,W23,AC23,AI23,AO23,AU23,BA23,BG23,BM23,BS23)+SUM(Q24,W24,AC24,AI24,AO24,AU24,BA24,BG24,BM24,BS24))/2*(P_bleed_res_out*Bleed__sufficient_platelets_dec+Interim!$E$132*'Utilities AEs'!$C$47)+((SUM(Markov!M23:BT23)-SUM(Q23,W23,AC23,AI23,AO23,AU23,BA23,BG23,BM23,BS23))+(SUM(M24:BT24)-SUM(Q24,W24,AC24,AI24,AO24,AU24,BA24,BG24,BM24,BS24)))/2*((1-Interim!$D$141)*(P_bleed_nonresp_out*Bleed__low_platelets_dec+P_bleed_nresp_inpat*'Utilities AEs'!$C$46)+Interim!$D$141*(P_bleed_res_out*Bleed__sufficient_platelets_dec+Interim!$E$132*'Utilities AEs'!$C$47))
+(Markov!$N$20*average(Markov!R23:R24)+Markov!$T$20*average(Markov!X23:X24)+Markov!$Z$20*average(Markov!AD23:AD24)+Markov!$AF$20*average(Markov!AJ23:AJ24)+Markov!$AL$20*average(Markov!AP23:AP24)+Markov!$AR$20*average(Markov!AV23:AV24)+Markov!$AX$20*average(Markov!BA23:BA24)+Markov!$BD$20*average(Markov!BH23:BH24)+Markov!$BJ$20*average(Markov!BN23:BN24)+Markov!$BP$20*average(Markov!BT23:BT24))*(FinalBleed-1)*((1-Interim!$D$141)*(~~P_bleed_nonresp_out*Bleed__low_platelets_dec+~~P_bleed_nresp_inpat*'Utilities AEs'!$C$46)+Interim!$D$141*(~~P_bleed_res_out*Bleed__sufficient_platelets_dec+~~Interim!$E$132*'Utilities AEs'!$C$47))