Comments on the Patient Access Scheme, and responses to the ERG report and Appraisal committee document

In this response the ERG has focused solely on those points which are potentially contentious or require clarification.

The following members of the ERG have contributed to this document

Clinical effectiveness:

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Summary of new evidence submitted

In response to the points raised by the appraisal committee the manufacturer submitted a revised set of analyses (presented in the 'Response to the appraisal consultation document on romiplostim'). These analyses have been further revised in a Patient Access Scheme submission for romiplostim. Accompanying this submission was a revised economic model incorporating the changes made when responding to the appraisal consultation document on romiplostim and the impact of a patient access scheme.

Clinical effectiveness

Comments on quality and quantity of evidence available

The manufacturer states that both the EMEA and International Consensus Report stressed the high quality of evidence for romiplostim. The ERG note however that the trial evidence was designed to assess efficacy and safety versus placebo and not against standard NHS practice, or given the acknowledged lack of consensus, several alternative NHS practices. In order to overcome this limitation the manufacturer has drawn comparisons against other active treatments using data from the literature. The value of such comparisons is limited by the indirect nature of the evidence available, which may suffer from biases of unknown magnitude and direction[1,2] and limited evidence base on the comparators (nb the ERG were not aware of any existing evidence that the manufacturer omitted from their original submission that would have had a material impact).

It is an issue for the appraisal committee to judge whether it is in the best interests of the NHS and the patients that the NHS treats to accept romiplostim on the basis of the underlying evidence available for this single technology appraisal.

Accounting for romiplostim responders and non-responders dosed beyond the maximum dose stated in the SPC and for censoring of patients in time to failure calculations

The approach taken by the manufacturer to account those individuals who were dosed beyond the SPC seems generally reasonable to the ERG.

The ERG note that these revised estimates do not address the point made in the ERG report that the existing analyses assume that patients who are censored have the same outcome as those for whom data were available. Arguably, those who are censored may not have the same outcomes and the ERG in our report presented two alternative analyses. In the first the ERG assumed that censored patients did not fail (a best case scenario) and in this

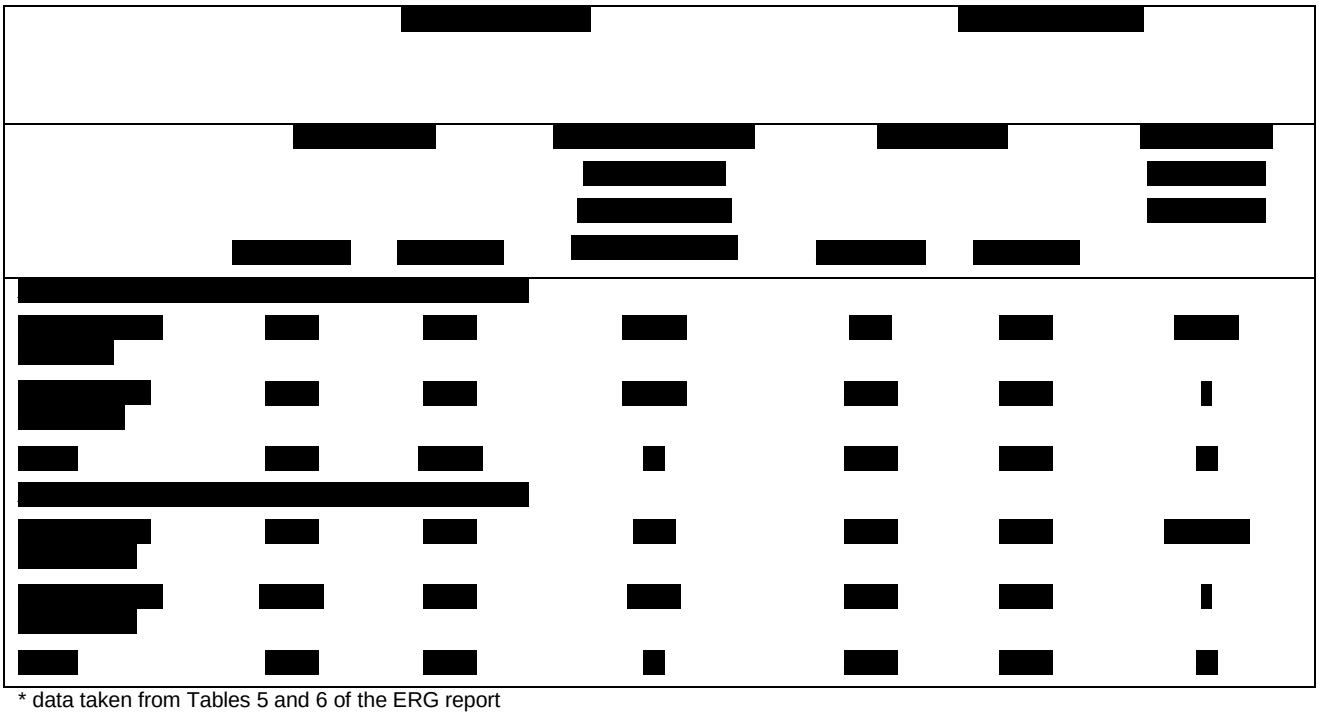
analysis the mean time to failure was estimated by the ERG as [redacted]. In the second it was assumed that all censored patients did fail (a worst case scenario) and this gave a mean time to failure of [redacted] (The manufacturer presented a mean time to failure of [redacted] in their model that accompanied the patient access scheme submission).

Mortality benefit associated with romiplostim

In the ACD (Section 4.10 and 4.12) it was noted that there was a mortality benefit estimated for romiplostim. There were no observed deaths in the trial therefore the risk of death was extrapolated from the risk of major bleeds. This survival benefit was a result of the decreased episodes of severe bleeding and therefore the presumed decrease in associated mortality. The manufacturer notes that a minority of patients are refractory and have persistently low platelet counts and that these patients have the highest risk of subsequent bleeding and mortality. The patients included in the romiplostim trials were judged by the manufacturer to be 'relatively' refractory and many had received 2 or more prior treatments. This raises questions about the relevance of the trial data to populate a model comparing sequences of treatments (an issue that will be considered further below). It also raises questions about the generalisability and applicability of the trial results to an NHS population of ITP patients.

The manufacturer states that the rates of bleeding and subsequent use of rescue medications were based upon the trial data. Based upon the data provided by the manufacturer the ERG confirms this. Table 1 below summarises the rates of bleeding per patient per 4 week period (4 weeks was chosen as the cycle length by the manufacturer in their economic model). While not presented in the table, and as noted above, the manufacturer also assumed that these bleeds would lead to an excess mortality. In every 4 week period 3.4% of those suffering bleeds requiring hospital treatment ([redacted] of the whole population suffer a bleed requiring hospitalisation) die.

Table 1 Evidence on the rates of bleeding based upon the romiplostim trial data



* data taken from Tables 5 and 6 of the ERG report

† data taken from the 'bleeding' data inputs sheet of the revised economic model submitted along with the "Patient Access Scheme Submission"

Source: manufacturer's submission and response to clarification queries document.

The clinical member of the ERG notes that of people requiring treatment in routine practice the rate of bleeding is not as high as the [redacted] every 4 weeks used in the model. Furthermore, most of these bleeds will be minor not requiring treatment. This suggests that the data may not generalisable to the majority of patients with ITP and would only be applicable to that proportion of patients with a similar elevated risk. It is unclear from the submission how the NHS could identify these patients should a decision favourable to the manufacturer be arrived at.

Cost-effectiveness

Comments on the calculation of the rebate to the NHS to compensate for the non-availability of 100 mcg vial

In the manufacturer's patient access submission the calculation of the rebate is presented in Table 1 of the submission. Calculations on the number of vials used are made for both splenectomised and non-splenectomised patients and for scenarios assuming both the availability and non-availability of 100 mcg vials. These calculations were based upon the

patient level data on dosing and assumed no sharing of vials. The two main assumptions made when making these assumptions were that:

- Dosages observed in the phase 3 trials are applicable to the population of NHS patients with ITP who have failed on at least one other treatment (the stated population for this appraisal). The extent to which the patients within the trials are sufficiently similar to the target population in the UK NHS is a matter for debate.
- The ratio of splenectomised to non-splenectomised patients is 1:1. The analysis conducted by the manufacturer suggests that there would be more wastage amongst non-splenectomised patients than splenectomised patients. However, in Table 8.1 of the manufacturer's original submission the manufacturer suggested that there would be less eligible patients in the non-splenectomised group than in the splenectomised group ([redacted]). If these proportions were used then the estimated rebate would be [redacted] depending upon whether the manufacturer's conservative or realistic assumptions are used. The ERG notes that these values are consistent with the proposed rebate.

Taking the manufacturer's analyses presented in Tables 4 and 5 of the Patient Access Scheme Submission at face value then the provision of a rebate would improve cost-effectiveness of romiplostim relative to a comparator. [redacted]

The ERG conducted an exploratory analysis in which the impact of a 10% increase in the average number of 250 mcg vials used was assumed. The 10% increase is arbitrary but was used to illustrate the sensitivity of the results to assumptions about how many vials per patient would be used in regular NHS practice (Table 2). It should be noted that this uncertainty may also mean that the manufacturer's data overestimate routine NHS dosages. In such a situation, other things being equal, the cost-effectiveness of romiplostim will improve.

Table 2 Sensitivity analysis around the average number of vials used

		Romiplostim	Active comparator	Marginal Costs	Marginal QALYs	ICER
Splenectomised						
Base case	Costs QALYs	[redacted] 12.38	[redacted] 11.35	£4743	1.03	£4615
Use of romiplostim vials 10% above trial values	Costs QALYs	[redacted] 12.38	[redacted] 11.35	£20,904	1.03	£20,340
Non-splenectomised						
Base case	Costs QALYs	[redacted] 11.93	[redacted] 10.41	£37,561	1.51	£24,795
Use of romiplostim vials 10% above trial values	Costs QALYs	[redacted] 11.93	[redacted] 10.41	£52,127	1.51	£34,410

Comments on model structure and sequence of treatments

The manufacturer notes that in an exploratory analysis conducted by the ERG all patients in the comparator arm were started on rituximab and that this was inconsistent with the romiplostim arm where only 59% of patients go onto rituximab after failure with romiplostim. The manufacturer goes on to acknowledge that an appropriate comparator could involve starting with an active treatment and in their response to the ACD (see Table 3.2 and the text immediately that table in the ACD response document) they outline alternative assumptions that could be used to define a comparator arm and the impact of these assumptions on cost-effectiveness. The ERG accept that alternative assumptions could be used to define the comparator treatment but notes that this debate misses the real issues which are the uncertainty over what the appropriate comparator should be and the assumptions the manufacturer has used to define their comparator intervention.

The model supplied by the manufacturer describes a sequence of treatments. The first treatment in this sequence is rituximab. If a patient does not start on rituximab then they start later on in the treatment sequence and have no prospect of ever receiving rituximab. Regardless of the results of the clinician survey conducted by the manufacturer the question is whether it is reasonable to exclude some potential treatments in the comparator arm while assuming romiplostim is used in 100% of patients in the romiplostim arm? (The ERG explores later the impact of changing the use of comparator treatments).

The implication of restricting the use of treatments is that it forces patients within the model to spend time on the very high cost and very poorly performing watch and rescue states. Any change in the model structure that prevents patients spending time in watch and rescue will improve the cost-effectiveness of the comparator treatment. In Table 3 below the ERG

reports the time spent in each treatment state for the analyses presented in Table 4 of the manufacturer's Patient Access Scheme submission (the manufacturer's revised base case following ACD response and PAS).

As can be seen from Table 3 the majority of time for all treatments is spent in Watch and Rescue. In the romiplostim arms of the model more time is spent on romiplostim treatment than all the other active treatments combined. This is due to romiplostim being the only treatment which 100% of patients can receive, and the cumulative effect of assumptions made about the effectiveness of alternative treatments and on the probabilities that they might be used.

Although not shown in Table 3 the structure of the model is such that after 1 year (i.e. 13 cycles) 16.4% of non-splenectomised patients have exhausted all active treatments and are in the final watch and rescue state compared to 1.3% of patients in the romiplostim arm. Similar data for splenectomised patients are 21.6% for active treatment arm and 3.3% for the romiplostim arm.

Table 3 Time spent on each management for splenectomised and non-splenectomised patients

Treatment	Non-splenectomised Time on treatment (years)		Splenectomised Time on treatment (years)	
	Romiplostim	Active comparator	Romiplostim	Active comparator
Romiplostim	[redacted]	0.00	[redacted]	0.00
Rituximab	0.52	0.57	0.52	0.57
Azathioprine	0.54	0.60	0.65	0.70
MMF	0.16	0.17	0.15	0.16
Cyclopsporine	0.03	0.03	0.03	0.03
Dapsone	0.36	0.40	0.37	0.41
Danazol	0.25	0.31	0.34	0.41
Cyclophosphamide	0.02	0.03	0.02	0.02
Vinca alkaloids	0.01	0.01	0.01	0.01
Watch and rescue	13.95	17.98	15.46	19.65
Total	[redacted]	**20.10**	[redacted]	**21.96**

These differences in time spent in the watch and rescue states between the romiplostim and the active comparator arm are important determinants of the differences in costs and QALYs and hence cost-effectiveness. The reason for this is that watch and rescue is assumed to have a relatively low effectiveness and a very high cost because all patients on watch and

rescue are assumed to have platelet counts below 50 x 10^9/l unless they have responded to rescue medication.

The impact of this with respect to life years and QALYs is:

- Patients, as noted above, with a platelet count of below 50 x 10^9/l have an increased risk of having a bleed requiring hospitalisation. Only hospitalised bleeds result in excess mortality and every 4 weeks approximately 0.1% of those on watch and rescue die.
- Patients with a platelet count below 50 x 10^9/l are assumed to have a lower quality of life (the manufacturer's crude pooling of time trade off and EQ-5D values suggest a difference of 0.035 between having a platelet count over 50 x 10^9/l and below 50 x 10^9/l). This difference in quality of life is a less important determinant of the difference in QALYs between romiplostim and an active treatment than the increased risk of mortality experienced by those in watch and rescue.

With respect to costs

- Patients who suffer a bleed that can be managed in out-patients have a [redacted] (non-splenectomised) and [redacted] (non-splenectomised) chance of receiving rescue medication. The cost per episode of this rescue medication is £4784 for those splenectomised and £5694 for those who have not had a splenectomy. To put this into context of the analyses presented in Table 4 of the manufacturer's Patient Access Scheme submission, on average splenectomised patients receiving the active comparator had:
    - 2.24 more episodes of rescue medication per year than the average romiplostim patient
    - 37.60 more episodes of rescue medication over the model time horizon than the average romiplostim patient
    - A net additional cost of rescue medication of [redacted] (undiscounted) compared with the average romiplostim patient over the time horizon of the model

Impact of changes in the use of rescue medication

Given the large chance of patients with less than 50 x 10^9/l needing rescue medication each 4 week cycle the ERG has performed exploratory analyses of the impact of reducing the use rescue medications. In these analyses the chance of receiving rescue medication has been reduced until it is no more than 75% of the level used in the base case analysis reported in Table 4 of the manufacturer's Patient Access Scheme submission (Table 4 of this

document). It should be noted that these analyses while reducing costs of rescue medication also, given the model structure, reduce survival and QALYs, as rescue medication is no longer used to the same extent to increase platelet counts to above 50 x 10^9/l.

As Table 4 shows costs reduce for both the romiplostim and active comparator arm but reduce more quickly for the active comparator and as a result the difference in cost increases as the use of rescue medications decrease. QALYs fall for both but the fall is greater for the active comparator arm and hence the difference in QALYs increases. Overall the ICER increases as the use of rescue medications fall, illustrating that the model is more sensitive to the changes in cost of using these medications than the effect of these medications on QALYs.

Table 4 Sensitivity analysis around the use of rescue medications

		Romiplostim	Active comparator	Marginal Costs	Marginal QALYs	ICER
Splenectomised						
Base case	Costs	[redacted]	[redacted]			
	QALYs	12.38	11.35	£4743	1.03	£4615
Rescue medications use 90% of base case	Costs	[redacted]	[redacted]			
	QALYs	12.25	11.16	£21,399	1.09	£19,547
Rescue medications use 80% of base case	Costs	[redacted]	[redacted]			
	QALYs	12.14	10.98	£37,309	1.16	£32,190
Rescue medications use 75% of base case	Costs	[redacted]	[redacted]			
	QALYs	12.08	10.89	£44,996	1.19	£37,807
Non-splenectomised						
Base case	Costs	[redacted]	[redacted]			
	QALYs	11.93	10.41	£37,561	1.51	£24,795
Rescue medications use 90% of base case	Costs	[redacted]	[redacted]			
	QALYs	11.89	10.34	£46,588	1.54	£30,173
Rescue medications use 80% of base case	Costs	[redacted]	[redacted]			
	QALYs	11.85	10.28	£55,418	1.57	£35,248
Rescue medications use 75% of base case	Costs	[redacted]	[redacted]			
	QALYs	11.84	10.25	£59,759	1.59	£37,682

Impact of changes to the effectiveness and use of comparator treatments

As noted above any change in the model that results in less time spent in the watch and rescue states improves the cost-effectiveness of the comparator. In Appendix 1 of the manufacturer's Patient Access Scheme Submission the manufacturer explored three

sensitivity analyses: (i) increasing the use of comparator treatments by 25%; (ii) increasing response time of comparators by 50%; and (iii) increasing the response rate of rituximab alone. These three sensitivity analyses address concerns that the use of comparator treatments might be too low and that the non-randomised non-comparative data used may be biased against the comparator treatments. The manufacturer reports that the ICERs for each of these three analyses would increase but would still all be below £35,000. The ERG has run an exploratory multi-way sensitivity analysis firstly by combining (i) and (ii) above (i.e. increasing the use of comparator treatments by 25% and increasing response time by 50%) and then by assuming that response rates for all the comparator treatments have been increased by 25%.

In these analyses the ICERs for both splenectomised and non-splenectomised populations increase but are less than (splenectomised) or just greater than (non-splenectomised) £30,000. However, when combining these sensitivity analyses with a reduction in the use of rescue medications the ICERs for both splenectomised and non-splenectomised patient groups increase beyond £45,000 (Table 5).

Comment on the estimation of utility values

In their revised analysis the manufacturer argues that it is appropriate to pool the utility scores obtained using the EQ-5D within the trials with time trade-off data obtained from a separate survey. One reason for this is that EQ-5D data from the trials is available on 125 patients while data on the time trade-off survey is available from 359 respondents. No consideration is given however as to whether it is appropriate to combine data from two different tools and two different samples (and no information has been provided on the time trade-off scenarios presented to respondents to help judge the applicability of these to the states modelled). The method for combining the two utility measures is a crude aggregation and as such it is arguable whether the EQ-5D data derived from the trials might be superior. The EQ-5D values are only available for some health states and to overcome this limitation the manufacturer compared the available EQ-5D values with the time trade-off values for the identical state to derive a scaling parameter. The scaling parameter was then used to rescale the time trade off valuations for those states where there was no EQ-5D valuation (see Table A1 in the manufacturer's Patient Access Scheme submission). The ERG has incorporated this change in utility values into the multi-way sensitivity analysis reported above and as Table 5 illustrates the ICERs for both the splenectomised and non-splenectomised groups are around £50,000.

Table 5 Results of multi-way sensitivity analysis around rates of comparator treatments use, effectiveness of comparators and health state utilities

		Romiplostim	Active comparator	Marginal Costs	Marginal QALYs	ICER
Splenectomised						
Base case	Costs	[redacted]	[redacted]			
	QALYs	12.38	11.35	£4743	1.03	£4615
(1) Increasing use of comparator treatments by 25% & response time by 50%	Costs	[redacted]	[redacted]			
	QALYs	12.59	11.65	£15,774	0.93	£16,934
(2) As (1) but also increasing response rates by 25%	Costs	[redacted]	[redacted]			
	QALYs	12.68	11.78	£19,960	0.89	£22,409
(3) As (2) plus use of rescue medications reduced to 80% of base case	Costs	[redacted]	[redacted]			
	QALYs	12.47	11.46	£49,347	1.00	£49,226
(4) As (3) plus substitution of scaled back utilities rather than pooled utilities	Costs	[redacted]	[redacted]			
	QALYs	11.77	10.79	£49,347	0.97	£50,690
Non-splenectomised						
Base case	Costs	[redacted]	[redacted]			
	QALYs	11.93	10.41	£37,561	1.51	£24,795
(a) Increasing use of comparator treatments by 25% & response time by 50%	Costs	[redacted]	[redacted]			
	QALYs	12.17	10.79	£44,321	1.38	£32,198
(b) As (a) but also increasing response rates by 25%	Costs	[redacted]	[redacted]			
	QALYs	12.26	10.94	£46,885	1.32	£35,413
(c) As (b) plus use of rescue medications reduced to 80% of base case	Costs	[redacted]	[redacted]			
	QALYs	12.20	10.83	£63,304	1.37	£46,213
(d) As (c) plus substitution of scaled back utilities rather than pooled utilities	Costs	[redacted]	[redacted]			
	QALYs	11.50	10.17	£63,304	1.33	£47,591

Comment an analysis of response time for romiplostim

In the ERG report it was noted that time to failure of romiplostim was calculated as the time from first exposure to romiplostim treatment to the time of discontinuation. Patients who had a last visit and were not recorded as being withdrawn from therapy were considered censored (Section 4.3.1, *Time to failure on romiplostim*). In the manufacturer's response to points for clarification (Amgen response to points for clarification, B6) best case and worst case scenarios were estimated under alternative assumptions about the outcomes for those patients whose data were censored. These analyses have not been replicated here but the

ERG has conducted an exploratory analysis using the data previously estimated as a worst case scenario for romiplostim (i.e. assuming that all those who withdrew from therapy ceased to respond to romiplostim). Substituting these data into the model gave an ICER of £18,654 for splenectomised patients (base case analysis ICER from the manufacturer's Patient Access Scheme submission was £4615) and £31,605 for non-splenectomised patients (base case £24,795). Table 6 reports this sensitivity analysis when it was combined with sensitivity analyses (4) and (d) from Table 5 above

Table 6 Multi-way sensitivity analysis around rates of use of comparator treatments, effectiveness of comparators, health state utilities and a worst case scenario for the duration of response to romiplostim

		With romiplostim	Without romiplostim	Marginal Costs	Marginal QALYs	ICER
Splenectomised	Costs	[redacted]	[redacted]			
	QALYs	11.02	10.79	£14,707	0.23	£64,646
Non-splenectomised	Costs	[redacted]	[redacted]			
	QALYs	10.49	10.17	£17,834	0.32	£55,470

Summary comments

In this document the ERG has tried to highlight a number of uncertainties that exist and important factors to bear in mind when making a judgement. In the analyses presented above the ERG show that potential combinations of events may increase ICERs beyond £30,000. How plausible these situations are is a judgement and below we highlight some of the factors that may be relevant for the appraisal committee to consider.

The stated objective of the manufacturers work is to make a case for the use of romiplostim where one or more comparator treatments have failed. The analyses consider a group of patients who can only receive some of the alternative treatments and even when they do receive an alternative treatment they only receive it briefly (see Table 3). The majority of survival time is spent in watch and rescue, which is high cost (because of the quantity of rescue medication used) and less effective (mainly because of the mortality from bleeding events, and lower quality of life when platelet counts are low). The ERG considers that the use of rescue medications may not reflect the experience of many people with ITP (although it acknowledges that it will almost certainly reflect the experience of some). Therefore, the following points need consideration:

- Is the very small amount of time spent receiving alternative treatments consistent with the experience of managing people with ITP in the NHS who have failed at least one

treatment? For example a systematic review of rituximab for ITP[3] demonstrated an overall response rate of 62.5% (95%CI 52.6-72.5) with a medium duration of response of 10.5 months (IQR 6.3-17.8). If it is not consistent then is the pattern of treatment consistent with a more severe patient group? And if it is how can they be defined so that the NHS could potentially target the use of romiplostim?

- Is the quantity of rescue medication (used on average 8.1 times per year in the active treatment arm for splenectomised patients and 4.5 time per year for non-splenectomised; rates for the romiplostim arm are 5.9 and 3 times respectively) consistent with the experience of the managing people with ITP in the NHS who have failed at least one treatment? For example if steroids were used for a rescue medication the recommended initial treatment length would be 21 days then a gradual dose reduction over the following 6-8 weeks. If it is not consistent is the pattern of use of rescue medication consistent with a more severe patient group? And if it is, how can they be defined so that the NHS could potentially target the use of romiplostim? This might be informed by a pooled analysis[4] which demonstrated a significant effect of age on the bleeding risk with those <40, 40-60 and >60 years having a yearly major bleeding risk of 0.025, 0.0725 and 0.719 respectively which leads to a risk of death of 0.004, 0.012 and 0.130 respectively in patients with a platelet count persistently below $30x10^6$/L.

With respect to effectiveness of interventions the evidence for romiplostim while coming from trials, unfortunately did not draw a comparison with an active treatment of relevance to the NHS. This meant that such comparisons had to be synthesised using non-randomised and non-comparative data. Such data are potentially biased. It is quite possible that the extent of this bias is sufficient to increase the ICERs beyond £30,000. Furthermore, the romiplostim trials have taken a standard approach to handling missing data i.e. they have assumed that the outcomes of those for whom data are missing are the same as those for whom data are available. This may overestimate the effectiveness of romiplostim. It is unlikely that all withdrawals will fail (some may simply not wish to continue in a trial but would otherwise be willing to continue treatment). However, if the proportion of failures amongst those who withdrew is higher than amongst those who contributed data for analysis then the ICER will increase.

- It is a matter for judgement as to whether these uncertainties are sufficiently important for ICERs estimated by the manufacturer to be considered unreliable and uninformative.

With respect to costs the main drivers are the use of romiplostim and the use of rescue medication. Increasing the use of romiplostim or reducing the use of rescue medication will increase the ICER. The judgement required about the use of rescue medication is

highlighted above. In terms of the use of romiplostim modest increase in the average use of vials of romiplostim increase the ICERs.

- A judgement is required as to whether the rates of usage of romiplostim reported in the trials and used in the economic model are representative of likely NHS practice.

References

1 Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F et al. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;7:1-173.

2 Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *Br Med J* 1998;317:1185-90.

3 Arnold DM, Dental F, Crowther MA, Meyer RM, Cook RJ, Sigoui R et al, Systematic Review: Efficacy and Safety of Rituximab for Adults with Idiopathic Thrombocytopenic Purpura. *Ann Intern Med* 2007;146:25-33.

4 Cohen YC, Djulbegovic B, Shamai-Lubovitz O, Mozes B. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. *Arch Intern Med*. 2000;160:1630-1638

Appendix 1: Table of model adjustments to generate the results in Tables 2-7 for the economic model evaluation.

All calculations undertaken and changes made were based upon the manufacturer's revised model which accompanied the Patient Access Scheme submission.

Adjustments for Tables 2, 4-7 (using settings tab cell I19 data input sheet to identify either the splenectomised or non splenectomised patient group)

Tab	Cell	Value in model (realistic approach, Table 4 of PAS)	Change made by ERG	Reason for the change
Table 2 sensitivity analysis around number of vial used				
[redacted]	[redacted]	[redacted] splenectomised [redacted] non-splenectomised	Value multiplied by 1.1	Explore impact of uncertainty in number of vials used
[redacted]	[redacted]	[redacted] splenectomised [redacted] non-splenectomised	Value multiplied by 1.1	
Tables 4 sensitivity analysis around use of rescue medications				
[redacted]	[redacted]	[redacted] splenectomised [redacted] non-splenectomised	Values multiplied by 0.9, 0.8. 0.75	Explore impact of lower use of rescue medications
Table 5 sensitivity analysis around rates of comparator effectiveness use, effectiveness and utilities				
Increasing use of comparator treatments	Inputs sheet R14 Rituximab R15 Azathioprine R16 MMF R17 Cyclosporine R18 Dapsone R19 Danazol R20 Cyclophosphamide R21 Vinca alkaloids	59% Rituximab 59% Azathioprine 37% MMF 4% Cyclosporine 48% Dapsone 7% Danazol 2% Cyclophosphamide 5% Vinca alkaloids	Values multiplied by 1.25	Replication of sensitivity analysis reported in Appendix 1 of the PAS
Increasing response time of comparators	I Inputs sheet, AO22 Rituximab AO23 Azathioprine AO24 MMF AO25 Danazol AO26 Dapsone AO27 Cyclosporine AO28 Cyclophosphamide AO29 Vinca alkaloids	Inputs sheet, 18.87 Rituximab 20.34 Azathioprine 5.68 MMF 12.91 S, 16.15 NS Cyclosporine 19.34 S, 20.34 NS Dapsone 143.9 S, 147.35 NS Danazol 26.99 Cyclophosphamide 1.4 Vinca alkaloids	Values multiplied by 1.5	Replication of sensitivity analysis reported in Appendix 1 of the PAS
Increasing response rates	Inputs sheet AM22 Rituximab AM23 Azathioprine AM24 MMF AM25 Danozol AM26 Dapsone AM27 Cyclosporine AM28 Cyclophosphamide AM29 Vinca alkaloids	57.70% 62.84% S 50% NS, Azathioprine 44% S, 56.52 NS MMF 60% S, 45.29% NS Danazol 50% Dapsone 63.16% S, 50% NS Cyclosporine 61.45% S, 70% Cyclophosphamide 53.40% S, 67% Vinca alkaloids	Value multiplied by 1.25	Reflection of potential extent of bias due to using non-randomised and non-comparative data to draw comparisons.

Alternative utility values	Inputs sheet CM11 Platelet > 50, no bleed CM12 Platelet > 50, OP bleed CM13 Platelet < 50, no bleed CM14 Platelet < 50, OP bleed CM15 Platelet < 50, IH bleed CM16 Platelet < 50, GI bleed CM17 Platelet < 50, other bleed	Inputs sheet Platelet > 50, no bleed 0.835 Platelet > 50, OP bleed 0.734 Platelet < 50, no bleed 0.800 Platelet < 50, OP bleed 0.732 Platelet < 50, IH bleed 0.038 Platelet < 50, GI bleed 0.540 Platelet < 50, other bleed 0.540	Revised values Platelet > 50, no bleed 0.794 Platelet > 50, OP bleed 0.670 Platelet < 50, no bleed 0.762 Platelet < 50, OP bleed 0.668 Platelet < 50, IH bleed 0.035 Platelet < 50, GI bleed 0.493 Platelet < 50, other bleed 0.493	Replication of sensitivity analysis reported in Appendix 1 of the PAS
Table 6 sensitivity analysis around outcomes for those censored due to withdrawal from duration of response analysis				
Alternative estimation of duration of romiplostim response	Inputs sheet, durability calculation accessed using response time tab D35 Alpha D36 Beta	 Alpha 0.81 Beta 103.17	 Alpha 1.57 Beta 19.46	To assess the implications of assuming those censored ceased to respond