RESPONSE TO THE APPRAISAL CONSULTATION DOCUMENT ON ROMIPLOSTIM
Confidential information is redacted

Executive Summary

We have carefully reviewed and assessed the Appraisal Committee's consideration of the evidence on romiplostim for the treatment of adults with chronic idiopathic (immune) thrombocytopenia purpura (ITP). We note that the Appraisal Committee considered the evidence for the *"relative effectiveness of romiplostim compared with other treatments is lacking"* and that *"wastage of vial contents would occur in practice and therefore the drug cost of romiplostim would be substantially higher than proposed in the manufacturer's submission."* We are disappointed by these conclusions and the resulting preliminary guidance not to recommend romiplostim. We welcome the opportunity to respond to the ACD, and in our response, we address key issues highlighted in the ACD and demonstrate that romiplostim is both a clinically and cost-effective treatment that offers a vital new therapeutic alternative in this life limiting and life threatening orphan condition.

We would like to underscore the debilitating nature of chronic ITP in patients with severe symptoms and high risk of bleeding (i.e. those for whom active treatment would be considered). The Appraisal Committee remark that the morbidity associated with *"chronic ITP may attract a social stigma associated with the appearance of bruises, and can limit lifestyle choices" and "anxiety about risk of bleeding can affect quality of life and a person's ability to undertake to travel and/or undertake leisure activities."* Evidence suggests that for this group of patients with severe symptoms or high risk of bleeding, ITP is a life threatening disease where limited therapeutic alternatives are available and where the need for effective treatments is highest[1,2].

We would like to emphasize that the clinical benefits of romiplostim have been demonstrated and replicated in two independent randomised clinical trials (RCTs). The EMEA positively considered this *"strength of evidence uncommon in an orphan condition"* and that *"the effect of romiplostim should be placed in the context of a life threatening disease where limited therapeutic alternatives are possible[3]."* Indeed, apart from romiplostim, there are no well-conducted RCTs for the active comparators considered in this appraisal. The recently published International Consensus Report on the Investigation and Management of Primary Immune Thrombocytopenia[4] has assigned romiplostim the highest grade of evidence among the active comparators based upon this high quality of evidence (Grade A recommendation, Evidence level Ib). It is noteworthy that the lead author and multiple co-authors of this Consensus Report are UK clinicians.

We would further like to note that we believe romiplostim to represent precisely the type of significant medical innovation, addressing a clear unmet clinical need, in a highly limited patient population, and with substantial promise of improving quality or length of life that the Department of Health and NICE are seeking to incentivise through development of the Innovation Pass.

Indeed, we believe that romiplostim as a first in class agent - the first protein peptibody to be approved by either the FDA or EMEA - and the first therapeutic developed specifically to address ITP, a seriously debilitating, orphan disease, would clearly meet the draft criteria proposed for the Innovation Pass. As such, we are disappointed that the Appraisal Committee does not appear to have taken into account this parallel development when appraising romiplostim and would urge the Committee to do so in their forthcoming deliberations.

Romiplostim also exemplifies the challenges faced by orphan medicines when seeking to demonstrate cost-effectiveness. The romiplostim data may be considered uncommonly strong for the purpose of regulatory approval[3], while the relative immaturity and volume of data poses significant difficulties in a cost-effectiveness setting. Again, we would urge the Appraisal Committee to carefully consider the drivers for any residual uncertainty around romiplostim cost-effectiveness, in the light of the Innovation Pass criteria, and acknowledge that uncertainty as a reasonable function of data immaturity.

Regarding the cost-effectiveness of romiplostim, we would like to address a number of key points raised in the ACD:

- We acknowledge that an appropriate comparator pathway could involve starting with an active treatment rather than 'watch and rescue'. However, we consider that this was implemented inconsistently in the sensitivity analysis presented in the ACD. Specifically, the proportion of patients starting with the active treatment (rituximab) in the comparator arm (100%) is not consistent with the proportion of patients who subsequently go onto receive this treatment in the romiplostim arm (59%)[5]. We have performed this analysis consistently by setting the proportion of patients who receive rituximab in the comparator arm equal to the proportion of patients who receive rituximab further down the treatment pathway in the romiplostim arm, with the proportion set consistently, but perhaps unrealistically, at 100% in both arms. This consistent analysis results in a smaller increase in the ICERs compared to the inconsistent analysis presented in the ACD. While we acknowledge that an appropriate comparator pathway could involve starting with an active treatment rather than 'watch and rescue' it is not clear why rituximab was selected as the sole active comparator (i.e. set at 100%). The recently published International Consensus report on the Investigation and Management of ITP[4] includes rituximab as one of the options for second line treatment following failure of standard initial therapy of corticosteroids. However, the International Consensus report does not recommend rituximab ahead of any other second line therapy. Indeed this report assigns a lower grade recommendation to rituximab (Grade B, Evidence level IIa) versus romiplostim which had the highest grade recommendation for any treatment relevant to this appraisal (Grade A recommendation, Evidence level Ib)[4]. Moreover, the suitability of rituximab as a safe treatment for ITP has recently been questioned following the publication of data on the development of multifocal leukoencephalopathy (PML) after

rituximab treatment[6]. This further questions the appropriateness of a rituximab as the sole comparator in the active treatment pathway. We therefore believe that the most clinically representative way of making this comparison would be to assume that a proportion of patients (<100%) in the comparator arm start on rituximab (those who do not start on rituximab would receive a proportion of the next active therapy in the pathway and so on) instead of 100% as assumed in the analysis presented in the ACD. This again resulted in smaller increases in the ICERs, compared to the analysis presented in the ACD.

- The sensitivity analysis presented in the ACD which increased the number of vials used per patient had a large effect on the ICERs, especially for the splenectomised group. We understand the concerns raised by the Appraisal Committee with regards to potential wastage and vial sharing. Below we present clear and detailed information on our dosing calculations and demonstrate that within the dosing limits stated in the Summary of Product Characteristics (SPC), and with the availability of a 100mcg vial, the average number of whole vials required per patient (allowing for wastage and no vial sharing) yields cost-effective ICERs.

- We agree that the cost of bone marrow tests and blood film assessment should be included in the cost of treating with romiplostim. In clinical studies, 3.69% (10/271) of subjects were reported to have bone marrow reticulin[7]. We conservatively assume that 10% of patients require a bone marrow biopsy in the model. Blood film assessments are recommended prior to starting romiplostim and may be required if a patient loses response to romiplostim. Therefore, we assume that two blood film assessments are required. Based on the assumption that 10% of patients are likely to require one-off bone marrow tests and that a total of two blood film assessments are required during their course of treatment, we demonstrate that the ICERs increase marginally and not by the extent presented in the ACD.

- We agree in principle on the use of EQ-5D data from our RCTs. However, the EQ-5D data from the trials were based on 125 patients pooled across placebo and romiplostim arms under the conservative assumption that there is no treatment effect on utility. In this instance, we believe that the time trade-off utility values based on a sample size of 359 people (almost three times larger than our trial) would significantly add to the strength of the utility data. Therefore, we postulate that it would be inappropriate to ignore these data in an area where such data is scarce. A pragmatic approach would be to pool the two sources of utility data in order to obtain more robust estimates of utility scores in ITP based on a larger sample as well as to minimize any bias resulting from pooling across arms of the RCTs. Below we present ICERs from revised analyses pooling the two sources of utility data.

- The multivariate exploratory scenario analysis presented in the ACD yields ICERs that increase to unacceptable levels. We demonstrate here that romiplostim remains a cost-effective option when each of the approaches described above are incorporated simultaneously.

The revised base case ICERs of between £21,306–£25,951 in the non-splenectomised group and £13,951–£31,060 in the splenectomised group, demonstrate that romiplostim remains a cost-effective treatment for adult chronic ITP patients.

We trust that the analyses we have presented on the factors considered by the Appraisal Committee to be key drivers of the economics will provide the Committee with reassurance that the cost-effectiveness case for romiplostim is sufficiently robust. We would suggest that NICE recommend romiplostim for use in adult chronic ITP patients where active therapy is warranted, i.e. in patients with severe symptoms or at high risk of bleeding.

1. Response to Questions Posed by the Appraisal Committee

We would first like to respond to the four questions posed by the Appraisal Committee, followed by our detailed response to the Appraisal Consultation Document (ACD).

i) Do you consider that all of the relevant evidence has been taken into account?

The Appraisal Committee may have misunderstood the debilitating nature of chronic ITP in patients with severe symptoms and high risk of bleeding (i.e. those for whom active treatment would be considered). The Appraisal Committee remark that the morbidity associated with *"chronic ITP may attract a social stigma associated with the appearance of bruises, and can limit lifestyle choices" and "anxiety about risk of bleeding can affect quality of life and a person's ability to undertake to travel and/or undertake leisure activities."* However, the ACD does acknowledge that active treatment is more likely to be considered for those people with severe symptoms or at high risk of bleeding. Therefore, there appears to be an inconsistency in the AC's understanding of the severity of chronic ITP. In order to clarify the severity of chronic ITP, we refer to the recently published International Consensus report on the investigation and management of ITP[4], which states that *"signs and symptoms of ITP vary widely. Many patients have either no symptoms or minimal bruising, while others experience serious bleeding, which may include gastrointestinal hemorrhage, extensive skin and mucosal hemorrhage, or intracranial hemorrhage."* Published literature provides further evidence that ITP patients who are refractory to currently available treatments and have a persistently low platelet count are the ones who appear to be at the highest risk of severe bleeding and mortality[1]. One study found a 60% increased mortality (with evidence of bleeding or infection as the cause of death) in a substantial number of ITP patients, illustrating that ITP is a serious and potentially life-threatening illness[2]. Moreover, we would like to point out that romiplostim was designated as an orphan medicine by the EMEA based on the combination of disease severity and rarity. Indeed, the EMEA considered that *"the effect of romiplostim should be placed in the context of a life threatening disease where limited therapeutic alternatives are possible*[3]*."* Therefore, we encourage the Appraisal Committee to reconsider their appraisal of romiplostim in light of this clarification.

ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

The clinical summary in the ACD does not appear to be a reasonable interpretation of the strength of the romiplostim efficacy evidence. The ACD highlights that the evidence for romiplostim was derived from *"two small placebo-controlled studies"*. It further states that there is no clinical trial evidence to demonstrate its relative effectiveness compared with other active treatments. We would like to highlight that romiplostim is an EMEA

designated orphan medicine and that the EMEA positively considered the *"strength of evidence uncommon in an orphan condition"* and that *"the effect of romiplostim should be placed in the context of a life threatening disease where limited therapeutic alternatives are possible*[3]*."* The phase III trials for romiplostim consisting of 125 patients are the largest controlled clinical trials in ITP patients relevant to this appraisal[4]. Romiplostim is also the only treatment among the active comparators listed in the scope of this appraisal to have such a strong level of evidence (two independent RCTs demonstrating clinical benefit in terms of platelet count) whereas studies for the active comparators consist mainly of uncontrolled case series. Further the phase III studies evaluated the efficacy (and safety) of romiplostim in a "real world" context as they allowed patients to receive concurrent therapies such as azathioprine and danazol[8]. The recent International Consensus Report on the Investigation and Management of Primary Immune Thrombocytopenia[4] acknowledges the excellent responses provided by romiplostim, its high quality of evidence (Grade A recommendation, Evidence level Ib) and recommends its use as a second-line therapy. We would also like to point out that there were several important factors that prevented our undertaking of direct head to head clinical trial comparisons with active treatments. Firstly, since there is no one international standard second line treatment as such, there would be no one universally agreed comparator[4]. Secondly, the limited efficacy and safety data available for the alternative treatments, most of which are unlicensed for ITP, would limit our ability to ethically compare with such treatments in a head to head trial. [redacted]

The burden of proof should rest upon our competitors to provide data on efficacy and safety of their products and it appears perverse that the Appraisal Committee have criticised romiplostim (the only treatment with robust trial data in this orphan condition) for the lack of available efficacy and safety data for our comparators.

The ACD summary of cost-effectiveness appears to be reasonable in terms of the factors considered by the Appraisal Committee to be key drivers of the economic case, but not in terms of the revised ICERs presented. We agree that the key factors considered by the Appraisal Committee (i.e. use of active therapy as initiation treatment in the comparator arm, change in the number of vials, inclusion of costs of additional tests required for romiplostim and use of non-RCT EQ-5D data), may all increase the ICERs of romiplostim from that presented in our original base case. However, we are of the view that the increases in the ICERs (from varying these factors) presented in the ACD are not an accurate reflection of the most plausible ICERs. This is due to the nature of the assumptions made and how the resulting changes have been

implemented within the economic model. The ACD noted that *"The one-way sensitivity analysis that had most effect on the ICER was an adjustment of drug costs to account for vial wastage that would occur in practice, based on the smallest available vial size of 250 micrograms."* We understand the concerns raised in the ACD around this key driver, and in response, have provided detailed clarification and analysis of the number of whole vials required per patient based on the trial data. We have undertaken further analysis of our trial data to demonstrate that within the dosing limits stated in the SPC, and with the availability of a 100mcg vial, the average number of whole vials required per patient (which is based on whole vials for each patient, summed and then averaged across all patients with no vial sharing and with all unused product discarded) is between 0.99–1.04 250mcg vials per non-splenectomised patient and between 1.39–1.49 250mcg vials per splenectomised patient. The revised base case analysis using this more appropriate and clinically relevant calculation of the average number of whole vials required per patient results in ICERs that fall within the acceptable threshold range.

iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

We believe that the provisional recommendations may not represent a complete, clear and balanced assessment of the evidence presented and hence may not constitute a suitable basis for the preparation of guidance to the NHS. We have considered very carefully the exploratory scenario analyses presented in the ACD and made further changes to our economic model based on these analyses. The revised base case that incorporates our approach to all key assumptions (considered by the Appraisal Committee to be key drivers of the economics) indicates that romiplostim is a cost-effective therapy, for both the splenectomised group and the non-splenectomised group. Based on the analyses we have presented on the factors considered by the Appraisal Committee to be key drivers of the economics, we would like to request the Appraisal Committee to recommend the use of romiplostim in adult chronic ITP patients where active therapy is warranted, i.e. in patients with severe symptoms or at high risk of bleeding.

iv) Are there any equality related issues that need special consideration that are not covered in the ACD?

None.

2. Clinical Effectiveness of Romiplostim for Treatment of ITP

In the Consideration of Evidence section, the Appraisal Committee noted that the evidence for romiplostim was derived from two small placebo-controlled RCTs and that there is no clinical trial evidence to demonstrate its relative effectiveness compared with other active treatments. Our detailed response to this issue is provided below.

ACD Section 4.5

"It was mindful that evidence was derived from two small placebo-controlled RCTs."

"The Committee was, however, mindful that these two RCTs did not provide clear evidence about the relative effectiveness of romiplostim compared with the active comparator treatments listed in the scope for this appraisal."

"The Committee concluded that although there is evidence that romiplostim is more clinically effective than placebo, and that in the opinion of clinical specialists the technology has advantages over other active treatments, there is no clinical trial evidence to demonstrate its relative effectiveness compared with other active treatments."

Romiplostim is the first treatment specifically developed and licensed for ITP. It is a novel, first in class, thrombopoiesis stimulating protein that has been shown to increase platelet counts in ITP patients. Stimulation of platelet production by romiplostim provides a new therapeutic option for patients with ITP.

Romiplostim was designated as orphan medicinal product EU/3/05/283 on 27 May 2005 and the statement from the CHMP assessment report sums up the high quality of evidence for romiplostim, *"The benefits of romiplostim in terms of platelet count have been demonstrated and replicated in two independent randomised clinical trials. This strength of evidence is uncommon in an orphan condition like ITP and the effect of romiplostim should be placed in the context of a life threatening disease where limited therapeutic alternatives are possible[3]."* The recent International Consensus Report on the Investigation and Management of Primary Immune Thrombocytopenia[4] acknowledges the excellent responses provided by romiplostim, its high quality of evidence (Grade A recommendation, Evidence level Ib) and recommends its use as a second line therapy. This was the highest quality of evidence for any treatment relevant to this appraisal. Moreover, no other treatment in the International Consensus Report[4] received a higher grading than romiplostim. Therefore romiplostim is the only treatment among the active comparators listed in the scope of this appraisal to have such a strong level of evidence whereas studies for the active comparators consist mainly of uncontrolled case series.

Our romiplostim trial design was discussed extensively with the FDA and CHMP, and amongst global ITP experts (including a leading UK clinical expert) whom participated in the trial. The

phase III trials enrolled a 'real world' adult splenectomised and non-splenectomised ITP population that had received considerable prior ITP treatment. In addition, the trials also evaluated the efficacy and safety of romiplostim in a 'real world' context as patients were allowed to receive other active therapies (prednisone, azathioprine, danazol) during the trial. Given that most active treatments for ITP are used outside of their licensed indications (rituximab, danazol, ciclosporin, dapsone, cyclophosphamide and mycophenolate mofetil), it would be very challenging to conduct a head to head trial comparing romiplostim with an active treatment. Such a trial may have ethical implications, given that the efficacy, and especially the safety, of unlicensed treatments such as rituximab are unproven. Indeed the suitability of rituximab as a safe treatment for ITP has recently been questioned following the publication of data on the development of progressive multifocal leukoencephalopathy (PML) after rituximab treatment[6]. Further, designing a trial with an active comparator would be very challenging as there is no single standard treatment pathway used as routine practice in the UK as noted in Section 4.3 of the ACD*, "It heard from clinical specialists that the pathway of care for ITP would vary depending on individual person's circumstances, and that no single standard treatment pathway could be defined as routine practice with confidence."*

To conclude, we would like to emphasize both the EMEA and International Consensus Report high grading of the quality of the evidence for romiplostim[3,4]. It appears perverse to 'penalize' the strength of clinical data of romiplostim due to uncertainty resulting from limited and poor quality data of active comparators. We would like to request that the Appraisal Committee reconsider the strength of evidence for romiplostim in light of the factors outlined above.

3. Cost Effectiveness of Romiplostim for Treatment of ITP

The Appraisal Committee noted that several assumptions in the manufacturer's base case resulted in the underestimation of the cost per QALY gained. The analyses we have conducted on the assumptions considered by the Appraisal Committee to be key drivers of the economics are detailed below.

ACD Section 4.7

"The Committee did not consider the manufacturer's base-case comparison with a care pathway starting with 'watch and rescue' to be an appropriate comparator for romiplostim because the population for whom romiplostim holds a marketing authorisation would be those for whom active treatment would be offered in current UK practice. The Committee considered an alternative scenario in which the comparator pathway was initiated with rituximab treatment."

We acknowledge that appropriate comparator pathways could be those starting with active treatment rather than 'watch and rescue' (W&R). The Appraisal Committee considered an alternative scenario in which the comparator treatment pathway was initiated with rituximab treatment. However, we believe that this scenario was implemented inconsistently in the sensitivity analysis presented in the ACD. The treatment pathway in the economic model for our base case, the inconsistent analysis presented in the ACD and our consistent analysis are outlined in Table 3.1. It is evident from Table 3.1 that the analysis presented in the ACD may have biased the ICERs of romiplostim upwards by assuming that only 59% (based on Amgen conducted physician survey)[5] of patients go on to receive rituximab in the romiplostim treatment pathway versus 100% of patients who receive rituximab in the comparator pathway. This reduces the overall efficacy in the romiplostim pathway due to fewer patients going on to receive rituximab. In effect, the pathway of care should be seen as romiplostim ahead of, rather than instead of, rituximab (as in our original submission where the pathway of care was romiplostim ahead of W&R).

We have performed this scenario analysis consistently by keeping the proportion of patients who receive rituximab in the comparator pathway equal to the proportion of patients who receive rituximab in the treatment pathway in the romiplostim arm, with the proportion of patients treated with rituximab set at 100% in both arms. This resulted in a smaller increase in the ICERs, £21,674 in the inconsistent analysis in the ACD versus £18,258 in our consistent analysis in the non-splenectomised group and £29,771 in the inconsistent analysis in the ACD versus £21,343 in our consistent analysis in the splenectomised group.

Table 3.1: Scenario where treatment is initiated with Rituximab for all patients

Base Case:
Romiplostim Arm
Romiplostim (100%) → W&R[1] → ***Rituximab (59%)*** → W&R[1] → Next Active Treatments

Comparator Arm
W&R (100%)→ ***Rituximab (59%)*** → W&R[1] → Next Active Treatments

Inconsistent Analysis Presented in the ACD:
Romiplostim Arm
Romiplostim (100%) → W&R[1] → ***Rituximab (59%)***→ W&R[1]→ Next Active Treatments

Comparator Arm
Rituximab (100%) → W&R[1] → Next Active Treatments

Our Consistent Analysis (In Response to Inconsistent Analysis Presented in the ACD):
Romiplostim Arm
Romiplostim (100%) → W&R[1] → ***Rituximab (100%)*** → W&R[1] → Next Active Treatments

Comparator Arm
Rituximab (100%) → W&R[1]→ Next Active Treatments

[1] All patients (100%) who fail active therapy move on to a period of W&R before the next active therapy.

While we acknowledge that an appropriate comparator pathway could involve starting with an active treatment rather than 'watch and rescue', we believe that the most clinically representative way of making this comparison would be to assume that a proportion of patients (<100%) in the comparator arm start on rituximab instead of 100% as assumed in the analysis presented in the ACD. The recently published International Consensus report on the Investigation and Management of ITP[4] includes rituximab as one of the options for second line treatment following failure of standard initial therapy of corticosteroids. However, the International Consensus report does not recommend rituximab ahead of any other second line therapy. We therefore assume that 59% of patients start on rituximab treatment (based on Amgen conducted physician survey results detailed in Table 7.1 of our original submission)[5]. In the economic model, this would entail, as per the ACD presented analysis, the removal of W&R as the initial comparator in the comparator arm; instead of assuming that 100% of patients then start on rituximab, we assume that 59% of patients start on rituximab treatment and the treatment pathway then continues as per the base case presented in our original submission. This means that the remaining 41% who do not start on rituximab would receive a proportion of the next active therapy in the pathway, i.e. azathioprine, and the proportion of patients who do not receive azathioprine would receive a proportion of the next active therapy (mycophenolate mofetil) and so on through the care pathway. All patients who fail rituximab (or any of the other active therapies) move on to a period of W&R between each active treatment. Table 3.2 illustrates our revised base case.

We feel that this would be more representative of and consistent with UK clinical practice as there is no single standard treatment pathway used as routine practice in the UK. This is noted by the Appraisal Committee in Section 4.3 of the ACD*, "It heard from clinical specialists that the pathway of care for ITP would vary depending on individual person's circumstances, and that no*

single standard treatment pathway could be defined as routine practice with confidence." This is also noted in the International Consensus report, *"physicians are required to make individual judgements about the nature of second line treatment based on bleeding history, comorbidities, patient expectations and compliance[4]."* We therefore undertook a revised analysis using this approach, which is more representative of and consistent with UK clinical practice. This revised analysis resulted in smaller increases in the ICERs than either the inconsistent analysis presented in the ACD or our more consistent analysis described above. The resulting ICERs were £21,674 in the inconsistent analysis in the ACD, £18,258 in our consistent analysis versus £16,322 in our revised base case analysis in the non-splenectomised group and £29,771 in the inconsistent analysis in the ACD, £21,343 in our consistent analysis versus £17,763 in our revised base case analysis in the splenectomised group.

Table 3.2: Scenario where treatment is initiated with Rituximab for a proportion of patients

Base Case:
Romiplostim Arm
Romiplostim (100%)→ W&R[1] → ***Rituximab (59%)*** → W&R[1] → Next Active Treatments

Comparator Arm
W&R (100%)→ ***Rituximab (59%)*** → W&R[1] → Next Active Treatments

ACD Presented Analysis:
Romiplostim Arm
Romiplostim (100%) → W&R[1]→ ***Rituximab (59%)*** → W&R[1] → Next Active Treatments

Comparator Arm
Rituximab (100%) → W&R[1]→ Next Active Treatments

Our Revised Base Case Analysis:
Romiplostim Arm
Romiplostim (100%)→ W&R[1] → ***Rituximab (59%)*** → W&R[1] → Next Active Treatments

Comparator Arm
Rituximab (59%)[2] → W&R[1] (for all patients who fail rituximab) → Next Active Treatments (for the 41% of patients who do not start on rituximab).

[1] All patients (100%) who fail active therapy move on to a period of W&R before the next active therapy.

[2] Only a proportion of patients receive rituximab as first line therapy; patients who do not receive rituximab, move on to the next active therapy and so on until all active therapies have been tried. The usage of each active treatment is based on the Amgen conducted Physician survey detailed in Table 7.1 of our original submission[5].

ACD Section 4.8 & 4.9

"It noted that the median dose used in the small RCTs was 3 micrograms/kg for splenectomised patients and 2 micrograms/kg for non-splenectomised patients, but was mindful that the average dose that would be used in clinical practice is unknown."

"The Committee agreed that, in practice, it is likely that there will be wastage from each vial and that vial sharing would not occur."

"The Committee was persuaded that the availability of a smaller vial size would increase the flexibility of dosing, reduce wastage and consequently improve the overall cost effectiveness of romiplostim."

The sensitivity analysis presented in the ACD which increased the number of vials used per patient had a large effect on the ICERs, especially for the splenectomised group. We understand the concerns raised by the Appraisal Committee with regards to potential wastage and vial sharing. Below we present clear and detailed information on the dosing calculations and demonstrate that within the dosing limits stated in the Summary of Product Characteristics (SPC)[7], and with the availability of a 100mcg vial, the average number of whole vials required per patient results in ICERs that fall within the acceptable threshold range.

In the base case of our original submission, the economic model assumed that an average patient would require an average of 0.93 and 1.38 of the 250mcg vial in the non-splenectomised and splenectomised groups respectively. The average number of vials stated here takes into account wastage (assuming that all unused product is discarded) and does not assume vial sharing. We apologise if this was not clear in our original submission and acknowledge that this may have led to misinterpretation by the Appraisal Committee who appear to have assumed that the average number of vials was based on patients using only a proportion of a whole vial, thereby excluding any wastage by assuming vial sharing, instead of whole vials with no vial sharing as was the case. To elucidate, we would first like to provide a detailed and clear explanation of the methodology that was used to calculate the average number of vials required per patient.

Methodology used for calculating average number of vials required per patient

The average number of vials was calculated from our trial data, using actual doses administered each week from week 13 to end of the study at week 24, avoiding the initial titration period for romiplostim. This should be viewed as a conservative approach as the exclusion of lower doses during the titration period from weeks 1 to 12 would have the effect of increasing the average dose (and number of vials required) of romiplostim per patient. For each patient, the number of whole vials required per weekly dose was ascertained. The number of whole vials needed to meet each weekly dose for each individual was summed across week 13 to week 24 to obtain an

average number of whole vials per patient which may not result in a whole number of vials calculated given the law of averages (e.g. the average (mean) of 1 whole vial for Week X and 2 whole vials for Week Y is 1.5 vials). This average (mean) number of vials per patient (which was based on averaging the whole vials required for each weekly dose from week 13 to week 24) was summed across all patients to obtain an average (mean) number of vials needed for an average (mean) patient. Table 3.3 provides an example of this dosing calculation (please note that this is a hypothetical example and is not based on actual trial data).

The hypothetical example presented in Table 3.3 assumes the availability of 100mcg vial. Therefore, depending in the dose required, any combination of full 100mcg vials and full 250mcg vials can be used to minimize wastage. As romiplostim is linearly priced (constantly priced per mcg across vial sizes), the combination of 100mcg and 250mcg vials required can be expressed solely in terms of the number of 250mcg vials required as shown in the table below.

Table 3.3: Hypothetical example of average number of whole vials required assuming 250mcg & 100mcg vials are available

	Wk 13	**Wk 14**	**Wk 15**	**Wk 16**	**Wk 17**	**Wk 18**	**Wk 19**	**Wk 20**	**Wk 21**	**Wk 22**	**Wk 23**	**Wk 24**	**Average No. Vials**
Patient 1													
Dose	225	225	335	335	335	335	335	335	335	335	335	335	
Vials 250mcg	1	1	1	1	1	1	1	1	1	1	1	1	1
Vials 100mcg	0	0	1	1	1	1	1	1	1	1	1	1	0.83
Patient 2													
Dose	200	200	200	200	200	200	200	345	345	345	345	345	
Vials 250mcg	0	0	0	0	0	0	0	1	1	1	1	1	0.42
Vials 100mcg	2	2	2	2	2	2	2	1	1	1	1	1	1.58
Average no. of 250mcg vials required for all patients													***0.71*** *((1+0.42)/2)*
Average no. of 100mcg vials required for all patients													***1.21*** *((0.83+1.58)/2)*
Average no. of vials required for all patients when expressed in terms of 250mcg vials													***1.19 (0.71+ ((1.21*100)/250))***

Base case approach in our original submission

The analysis presented in the base case in our original submission used the methodology illustrated in the hypothetical example in Table 3.3 to derive the average number of whole vials needed for an average person. It assumed an overfill of the vials to allow for dosing flexibility in clinical practice, i.e. providers may use a 250mcg vial to dose a patient requiring up to 300mcg and a 100mcg vial to dose a patient requiring up to 130mcg. As explained in our submission, the original analysis also assumed the availability of 100mcg vial and a maximum dose of 10mcg/kg as stated in the SPC.

Revised base case approach in this response

In our revised base case presented in this response, we have retained the methodology used to derive the average number of whole vials needed for an average person as described in the hypothetical example in Table 3.3. However, we have approached the dosing calculations differently to those presented in the base case in our original submission. We have done this in order to obtain a more appropriate and clinically relevant calculation of the average dose and resulting number of whole vials based on our trial and what would likely occur in UK clinical practice.

We took the following approach in the revised base case:

1. We conservatively assume no overfill, i.e. a 250mcg vial delivers 250mcg and no more and 100mcg vial delivers 100mcg and no more.

2. We appropriately account for romiplostim non-responders who were dosed beyond the maximum dose stated in the SPC[7] in our revised dose calculations. Upon further analysis of our trial dosing data, we ascertained that 6 of the 42 patients in the splenectomised arm and 2 of the 41 patients in the non-splenectomised arm were dosed above and beyond the maximum stated dose of 10mcg/kg in the SPC (the trial allowed patients to be dosed up to 15mcg/kg, but as little clinical benefit was deemed to be observed at doses above 10mcg/kg the maximum dose was subsequently reduced to 10mcg/kg in the SPC[7]). We also ascertained that 5 of the 6 splenectomised patients who were dosed above the maximum dose stated in the SPC were non-responders and were recorded as such in the efficacy measure of overall platelet response reported in our phase III trials and used in our economic model. Similarly, 1 of the 2 non-splenectomised patients who were dosed above the maximum dose stated in the SPC was a non-responder and so was recorded as such in the analysis of overall platelet response. In brief, the overall platelet response efficacy endpoint for romiplostim in the economic model, 88% (36/41) in the non-splenectomised group and 79% (33/42) in the splenectomised group, already accounted for non-responders who were dosed above the maximum dose stated in the SPC (i.e. these patients were included in the denominator but not in the numerator of the overall platelet response results reported in our phase III trials[8]). In our original base case in the economic model, we had appropriately

accounted for non-responders who were dosed above the maximum stated in the SPC in our efficacy endpoint so as not to overestimate the efficacy of romiplostim (non-responders stop treatment with romiplostim and move on to the next treatment at the end of each cycle). However, we had inappropriately included these non-responders in our dose calculations for the entire duration of the model (rather than until they discontinued treatment due to non-response) thereby significantly overestimating the dose and costs of romiplostim. In clinical practice, patients who do not respond would not be titrated to a dose above the maximum stated in the SPC and mostly certainly would not be continued long-term on a dose above the maximum stated in the SPC. We therefore believe that it is both consistent and clinically appropriate to account for non-responders in the dose and cost calculations (i.e. capping their dose at the maximum stated in the SPC only while they remain on treatment), just as we do for efficacy.

3. We appropriately account for romiplostim responders who were dosed beyond the maximum dose stated in the SPC[7] in our efficacy and dose calculations. As explained earlier, 6 of the 42 patients in the splenectomised arm and 2 of the 41 patients in the non-splenectomised arm were dosed above and beyond the maximum stated dose of 10mcg/kg in the SPC. 1 of the 6 splenectomised patients and 1 of the 2 non-splenectomised patients who were dosed above the maximum dose stated in the SPC were recorded as responders in the analysis of the overall platelet response efficacy endpoint reported in our phase III trials. In our revised base case, we include the doses required for these patients in the dosing calculations and we cap their dose at the maximum stated dose in the SPC. This would reflect clinical practice, as patients would not be titrated to a dose above the maximum stated in the SPC and certainly would not be continued long-term on a dose above the maximum stated in the SPC. As the doses for these 2 patients were capped at the maximum stated in the SPC, we conservatively ignore their responses and classify them as non-responders by adjusting the overall response for romiplostim downwards. The revised overall response rates are lower at 85% (35/41) versus 88% (36/41) in the base case for non-splenectomised group and 76% (32/42) versus 79% (33/42) in the base case for splenectomised group. We consider this an extremely conservative approach as we have included these patients in the dose and cost calculation for the entire duration of treatment in the model with their dose capped at maximum stated in the SPC, but have modelled them as non-responders thereby underestimating the efficacy of romiplostim observed in our trials. Given the extremely conservative nature of this approach, we have also conducted an alternative base case scenario analysis where we more appropriately account for these patients (i.e. responders who were dosed beyond the maximum dose stated in the SPC) in the dose and cost calculations. These responders only achieved their overall response after they had been dosed to beyond the maximum stated in the SPC, but in clinical practice, patients would not be dosed beyond the maximum stated in the SPC. Therefore we have conducted a more realistic alternative base case scenarios analysis where we assume that these patients

discontinue treatment with romiplostim and move on to the next treatment at the end of the cycle. This is consistent with the efficacy analyses as we ignore their responses and classify them as non-responders as explained in the preceding paragraph.

4. We assume the availability of the 100mcg vial as was assumed in the original base case. The Appraisal Committee *"was persuaded that the availability of a smaller vial size would increase the flexibility of dosing, reduce wastage and consequently improve the overall cost effectiveness of romiplostim."* We agree with this and demonstrate that cost effectiveness is indeed improved with the availability of the 100mcg vial. We assume no overfill, allow for wastage, assume no vial sharing and adjust for the patients dosed above the maximum dose stated in the SPC[7] as explained in points 2 and 3 above. In the conservative approach (where we assume that the 2 patients who needed to be dosed above the maximum stated in the SPC in order to achieve their response, do not stop treatment with romiplostim at the end of the cycle, and are included in the dose and cost calculation for the entire duration of treatment in the model with their dose capped at maximum stated in the SPC), the average (mean) number of whole vials required by an average patient is 1.50 100mcg vials plus 0.44 250mcg vials per non-splenectomised patient and 1.76 100mcg vials plus 0.78 250mcg vials per splenectomised patient. In the more realistic alternative base case scenario (where we assume that the 2 patients who needed to be dosed above the maximum stated in the SPC in order to achieve their response, discontinue treatment with romiplostim and move on to the next treatment at the end of the cycle), the average (mean) number of whole vials required by an average patient is 1.51 100mcg vials plus 0.38 250mcg vials per non-splenectomised patient and 1.69 100mcg vials plus 0.68 250mcg vials per splenectomised patient. As romiplostim is linearly priced (constantly priced per mcg across vial sizes), this can be expressed solely in terms of the number of 250mcg vials required (e.g. 1.50 100mcg vials can be converted into number of 250mcg vials by multiplying it by (100/250), which yields 0.60 250mcg vials). Thus the average number of 250 mcg vials required in the conservative scenario is 1.04 (0.60 + 0.44) per non-splenectomised patient and 1.49 (0.78 + 0.71) per splenectomised patient when expressed in terms of 250mcg vials. In the more realistic alternative base case scenario, the average number of 250 mcg vials required is 0.99 (0.61 + 0.38) per non-splenectomised patient and 1.35 (0.68 + 0.67) per splenectomised patient when expressed in terms of 250mcg vials. [redacted]

We present a revised base case that incorporates the approach described above. All patients (including non-responders and patients dosed above the maximum stated in the SPC) enter the model at the start. The dose calculation includes all patients assuming no overfill, allows for

wastage, assumes no vial sharing and assumes the availability of the 100mcg vial. It also caps the maximum dose at 10mcg/kg as stated in the SPC as in clinical practice patients would neither be titrated up to nor continued on a dose above the maximum stated in the SPC. This cap applies to the 6 patients in the splenectomised group and the 2 patients in the non-splenectomised group were dosed above the maximum stated dose in the SPC, as described earlier. Overall platelet response is assessed at the end of the cycle; 85% (35/41) and 76% (32/42) respond in the non-splenectomised and splenectomised groups respectively with non-responders discontinuing romiplostim treatment and responders remaining on romiplostim treatment. The response rates are lower than that reported in the phase III trials and used in our original base case model (88% and 79% in non-splenectomised and splenectomised groups respectively) as we have conservatively classified 2 responders who were dosed above the maximum stated in the SPC as non-responders but have included them in the dose and cost calculation with their dose capped at the maximum stated in the SPC as explained in point 3. In this extremely conservative scenario, the average number of whole vials required for the average patient who continues on romiplostim treatment at the end of the cycle is 1.04 250mcg vials per non-splenectomised patient and 1.49 250mcg vials per splenectomised patient when expressed in terms of 250mcg vials. In the more realistic alternative base case scenario, the average number of whole vials required for the average patient who continues on romiplostim treatment at the end of the cycle is 0.99 250mcg vials per non-splenectomised patient and 1.35 250mcg vials per splenectomised patient when expressed in terms of 250mcg vials. As noted earlier, the average number of vials required was calculated conservatively, using actual doses administered each week from week 13 to end of the study and excluding lower doses during the titration period up to week 12.

The revised base case results in a change in the ICER for the non-splenectomised group, £21,214 in the analysis presented in the ACD to between £20,381 (alternative scenario) and £25,024 (conservative scenario) in our revised base case and a decrease in the ICER for the splenectomised group, £91,406 in the analysis presented in the ACD to between £12,341 (alternative scenario) and £29,236 (conservative scenario) in our revised base case. The Appraisal Committee noted that *"the ICER was very sensitive to the assumption of average drug cost."* We acknowledge this concern and have demonstrated here that with our revised approach, the base case remains within the acceptable threshold range both in the conservative and the more realistic alternative base case scenario.

ACD Section 4.11

"The Committee considered other univariate sensitivity analyses undertaken by the ERG and noted that inclusion of revised costs such as those for a blood film assessment (which is required before treatment with romiplostim), bone marrow testing and the use of EQ-5D utility values from the romiplostim RCTs increased the ICERs for romiplostim compared with the base case."

"The Committee noted that an exploratory scenario analysis undertaken by the ERG using the manufacturer's model that combining all of the ERG assumptions (above) with accounting for vial wastage, using an active comparator and assuming a reduced frequency of physician visits resulted in ICERs for romiplostim of £37,300 per QALY gained in the non-splenectomised group and £131,000 per QALY gained in the splenectomised group."

Inclusion of Revised Costs

We agree that additional costs such as the cost of bone marrow tests and blood film assessment should be included in the costs of treating with romiplostim (these sensitivity analyses were presented in our response to clarification questions C6 and C7). The SPC states that in clinical studies for romiplostim, 3.69% (10/271) of subjects were reported to have bone marrow reticulin[7]. We have conservatively assumed that 10% of patients require a bone marrow biopsy in the model and we have estimated it to cost £1,000 per biopsy (we expect this to be a significant overestimation as we do not have a precise estimate for the cost of this biopsy). Although the SPC states that bone marrow biopsy should be performed only when there is a loss of efficacy, we have conservatively assumed that the cost of £100 (based on our assumption that 10% of patients would require bone marrow biopsy at £1,000 per biopsy) is incurred upfront in the first cycle in the economic model. This yields the same results as the analysis conducted by the ERG, £14,663 in the non-splenectomised group and £15,639 in the splenectomised group. Blood film assessments are recommended prior to starting romiplostim and may be required if a patient loses response to romiplostim. Therefore, we assume that two blood film assessments are required and have conservatively included the cost of two blood film assessments when patients start treatment, that is, in the first cycle of the economic model. These are estimated to cost approximately £100 in total (i.e. £50 each and again we expect this to be a significant overestimation as we do not have a precise estimate for the cost of these tests). This resulted in a smaller increase in the ICERs, £19,230 in the analysis presented in the ACD versus £14,663 in our revised base case in the non-splenectomised group and £22,068 in the analysis presented in the ACD versus £15,639 in our revised base case in the splenectomised group.

We believe this sensitivity analysis may have been mislabelled in the ACD Section 3.17 as *"the additional costs incurred by providing blood film tests before the treatment"* when it should have

been labelled as “reduced number of blood counts and clinic visits”. In the clarification questions that followed our original submission last year, question C8 requested that a sensitivity analysis be performed to reflect reduced number of blood counts and clinic visits in the comparator arm. We undertook this analysis assuming that all treatment options in the model except romiplostim would require half the number of lab tests to check blood counts every cycle (2 tests instead of 4 assumed in the base case) and half the number of clinic visits every cycle (1 clinician visit instead of 2 assumed in the base case) compared to our original base case. This analysis which assumed a reduced number of blood counts and clinic visits resulted in ICER of £19,230 in the non-splenectomised group and £22,068 in the splenectomised group, exactly matching that presented in the ACD under the mislabelled term *“the additional costs incurred by providing blood film tests before the treatment.”*

We propose that the scenario analysis we performed in response to the clarification question C8 was unrealistically conservative and greatly overestimated the monitoring costs for romiplostim as it assumed that all romiplostim patients would require 4 lab tests to check blood counts and 2 clinician visits every cycle for the entire duration of their treatment whilst the comparators (active treatments and W&R) would have the monitoring costs halved for every cycle. The SPC for romiplostim states that platelet counts should be assessed weekly until a stable platelet count has been achieved after which it should be assessed once monthly[7]. We assume that patients achieve stable platelet counts at the end of the trial period, i.e. 24 weeks. This is likely to be a conservative assumption as the trials showed that target platelet count was achieved within 2–3 weeks by over 50% of patients on romiplostim. We therefore present here a further scenario analysis to reflect a more realistic approach to monitoring costs as shown in Table 3.4. Here we assume that lab tests to check blood counts and clinician visits for romiplostim patients are reduced from 4 lab tests and 2 clinician visits to 1 lab test and 1 clinician visit every cycle (to be in line with the SPC) after 24 weeks. To be consistent, we also assume the all comparators require 1 lab test and 1 physician visit every cycle. We however conservatively assume this reduced level of monitoring for all comparators from the start of the model rather than from week 24 as is the case for romiplostim. This is a conservative assumption as increased monitoring is expected in the initial period when patients start on an active treatment, especially given the safety concerns around unlicensed comparators such as rituximab. Indeed, new safety concerns on the development of multifocal leukoencephalopathy after rituximab treatment would seem to indicate that close monitoring may be required[6].

Table 3.4: Monitoring frequency across all treatments

	Romiplostim	All Comparators
Our Original Base Case		
Lab tests to check blood counts	4 every cycle	4 every cycle
Clinician Visits	2 every cycle	2 every cycle
Our Response to Clarification Question C8		
Lab tests to check blood counts	4 every cycle	2 every cycle
Clinician Visits	2 every cycle	1 every cycle
Our Revised Analysis		
Lab tests to check blood counts	4 every cycle until platelet counts stabilise at 24 weeks & 1 every cycle thereafter	1 every cycle
Clinician Visits	2 every cycle until platelet counts stabilise at 24 weeks & 1 every cycle thereafter	1 every cycle

The revised base case (including bone marrow tests, blood film assessments for romiplostim and monitoring requirements as shown in Table 3.4) resulted in a small decrease in the ICERs, from £14,633 in our original base case to £13,160 in our revised base case in the non-splenectomised group and from £15,595 in our original base case to £14,233 in our revised base case in the splenectomised group.

EQ-5D Utility Values

We agree in principle on the use of EQ-5D data from the RCTs. The utility data from the UK members of the public was used in the model instead of the EQ-5D data from the RCT because it was based on a large sample of UK population, 359 (almost three times larger than our trial) compared to 125 patients in the two phase III trials. Further, these 125 patients were pooled across the placebo (n=42) and romiplostim arms (n=83) under the assumption that there is no treatment effect on utility. This is a conservative assumption and is likely to bias the cost-effectiveness estimates of romiplostim upwards since the phase III trials demonstrated a statistically significant absolute treatment effect on utility with romiplostim[9] (presented in Table 6.4.8 in the original submission). Therefore, the utility data from the survey of UK members of public was used not only because it had a much larger sample size but also to minimize any bias from pooling across the two arms of the phase III trials on the cost-effectiveness of romiplostim.

In this instance, we believe that the time trade-off utility values from UK members of the public, based on a larger sample size of 359 people, would significantly add to the EQ-5D data from the trial and minimize any bias resulting from pooling across arms of the RCTs. Instead of ignoring these data altogether in an area where such data is scarce (as was done in the analysis presented in the ACD), we believe that a pragmatic approach would be to pool the two sources of utility data in order to obtain more robust estimates of utility scores in ITP based on a larger sample as well as to minimize any bias resulting from pooling across arms of the RCTs. In this response, we have pooled the two sources of utility data to obtain more robust estimates of utility scores in ITP. In order to reduce bias, we pooled the utility data at an individual person/patient

level for the health states ‘platelet >50,000 and no bleed’ and ‘platelet <50,000 and no bleed’. The methodology we used to obtain a pooled utility value for each health state was to sum the individual patient level utility values in the two phase III trials with the individual person level utility values in the TTO study and divide by the total number of utility values observed. Table 3.5 presents the pooled utility values used in revised base case.

Table 3.5: EQ-5D Utility Values from RCT and Survey

State	EQ5D RCT Utilities	UK Survey Utilities	Pooled Utilities
Platelet > 50,000 and no bleed	0.794	0.863	**0.835**
Platelet > 50,000 and OP bleed	NA*	0.734	0.734
Platelet < 50,000 and no bleed	0.762	0.841	**0.800**
Platelet < 50,000 and OP bleed	NA*	0.732	0.732
Platelet < 50,000 and IH bleed	NA*	0.04	0.04
Platelet < 50,000 and GI bleed	NA*	0.54	0.54
Platelet < 50,000 and other bleed	NA*	0.54	0.54

OP – Outpatient; IH – Intracranial Haemorrhage; GI – Gastrointestinal; *Insufficient data to calculate these values and so assumed to be the same as the UK survey utilities

This resulted in a smaller increase in the ICERs, £16,503 in the analysis presented in the ACD versus £15,214 in our revised base case in the non-splenectomised group and £17,580 in the analysis presented in the ACD versus £16,215 in our revised base case in the splenectomised group.

Revised base case scenario combining our approach to all of the key points raised in the ACD

The multivariate analysis presented in the ACD shows that ICERs increase to levels above the acceptable threshold range. We demonstrate in this response that romiplostim remains a cost-effective option when our robust, consistent, and clinically relevant approaches to all of the key assumptions made in our revised analyses are incorporated simultaneously. Table 3.6 presents each of the sensitivity analysis presented in the ACD alongside our revised base case (incorporating all). In addition, it also presents the multivariate analysis incorporating all the key factors at the same time. In this analysis romiplostim remains a cost-effective option with ICERs between £21,306–£25,951 (more realistic versus conservative approach) in the non-splenectomised group compared to £37,290 presented in the ACD and between £13,951–£31,060 in the splenectomised group (more realistic versus conservative approach) compared to £131,017 presented in the ACD.

Table 3.6: Revised base case scenario combining our approach to all of the key points raised in the ACD

	ERG Analysis		Amgen Revised Base Case	
	Non-Splenectomised	**Splenectomised**	**Non-Splenectomised**	**Splenectomised**
Base Case in Submission	£14,633	£15,595	£14,633	£15,595
50% Decrease in Serious AEs[1]	£14,641	£15,608	£14,641	£15,608
Active Comparator[2]	£21,674	£29,771	£16,322	£17,763
Number of Vials[3]	£21,214	£91,406	£20,381-£25,024	£12,341-£29,236
Cost of Bone Marrow Test Included	£14,663	£15,639	£14,663	£15,639
Cost of Blood Film Assessments Included[4]	£19,230	£22,068	£14,663	£15,639
Reduced Number of Blood Counts & Clinician visits[5]	NA	NA	£13,160	£14,223
EQ-5D	£16,503	£17,580	£15,214	£16,215
Revised Base Case (incorporates our approach to all key drivers)	£37,290	£131,017	£21,306-£25,951	£13,951-£31,060

[1] This analysis is not discussed in this response as we agree with the results obtained in the sensitivity analysis conducted by the ERG where a 50% decrease in the utility values of the serious adverse events was assumed.

[2] Our revised base case assumes that a proportion of patients in the comparator arm, i.e. 59% (based on Amgen conducted physician survey), start on rituximab instead of 100%.

[3] Our revised base case considers two approaches – more realistic and conservative.

[4] We believe that this analysis may have been mislabelled in the ACD Section 3.17 *as "the additional costs incurred by providing blood film tests before the treatment"* when it should have been labelled as "reduced number of blood counts and clinic visits".

[5] The Amgen revised base case reflects the reduced frequency of lab tests to check blood counts and clinician visits (as shown in Table 3.4) and includes the additional costs of bone marrow test and blood film assessments.

4. Other Comments

In addition to the analyses we have conducted on the assumptions considered by the Appraisal Committee to be key drivers of the economics as detailed above, we have also addressed two points noted by the Appraisal Committee to contribute to the overall uncertainty around the ICERs presented.

ACD Section 4.10 & 4.12

"The Committee noted that the submitted model assumed a mortality benefit associated with romiplostim, with 2.92 and 2.03 estimated life years gained for the non-splenectomised and splenectomised group respectively. Specifically, the Committee noted that the economic modelling attributed a survival advantage to the romiplostim group as a result of avoiding severe bleeding episodes and the associated mortality."

"The Committee heard from the clinical specialists that this assumption was plausible, but there was substantial uncertainty about the magnitude of the effect and the validity of modelling data from short-term clinical trials to a lifetime horizon. "

"It heard from the ERG that the proportion of patients assumed in the model was approximately 70%, of whom approximately 60% required intravenous immunoglobulin, but that it was unclear what impact changes in these assumptions would have on the estimated cost per QALY gained when 'watch and rescue' was not the first-line comparator."

"The Committee then considered the monitoring assessments that the manufacturer assumed during 'watch and rescue'. It heard from clinical specialists that monitoring and provision of treatment is largely symptom dependent and may only be required infrequently."

Mortality benefit associated with romiplostim

Most patients with ITP respond to corticosteroid treatment with or without subsequent splenectomy and rarely need other immunosuppressive therapies[10], but a minority of ITP patients are refractory to currently available treatments and have a persistently low platelet count[1]. These chronic refractory patients appear to be at the highest risk of severe bleeding and mortality[11]. Indeed, the risk of severe bleeding has been estimated to increase with increasing patient age and among patients with platelet counts persistently $<30X10^9/l$[12]. A recently published paper observed a 60% increased mortality and found evidence of bleeding or infection as the cause of death in a substantial number of ITP patients[2].

The baseline characteristics of patients in romiplostim trials demonstrate that they were relatively refractory with a mean platelet level of below $20x10^9/l$ ($19x10^9/l$ in the non-splenectomised group

and $14x10^9$/l in the splenectomised group)[8]. Further a significant number of patients had received prior treatments [redacted]. It is in this 'more refractory' group of patients where the increased mortality due to bleeding is likely to be a substantial factor and it is in this group where an effective treatment that boosts platelet levels to 'safe' levels as romiplostim does could plausibly justify a survival advantage as a result of avoiding severe bleeding episodes and the associated mortality.

We agree that there could be uncertainty around the magnitude of the survival effect and the validity of modelling data from short-term clinical trials to a lifetime horizon. We acknowledge that this uncertainty arises from the time on treatment. In the economic model, the projection based on our clinical data suggests that patients stay on romiplostim for around [redacted]. We undertook a sensitivity analysis on our revised base case analysis varying the treatment duration from 1 to [redacted] to understand the impact of shorter treatment duration on the cost-effectiveness of romiplostim. In both splenectomised and non-splenectomised patients, romiplostim remained cost-effective across all treatment durations. In splenectomised patients, romiplostim was at its least cost-effective with ICER at £17,781 when treatment duration was shortened to one year. However, when compared to our original base case ICER of £15,595, this was only a small increase. Likewise, in non-splenectomised patients, romiplostim was least cost-effective with ICER of £16,491 when treatment duration was shortened to one year. When compared to our original base case ICER of £14,633, this was again only a small increase. In these analysis, the mortality benefit associated with romiplostim, decreased from 2.92 and 2.03 estimated life years gained to 0.42 and 0.29 for the non-splenectomised and splenectomised groups respectively. The smaller increase in life years in the latter scenario was matched by a smaller incremental cost of shorter treatment duration keeping the ICERs for romiplostim robust to changes in treatment duration and mortality benefit.

Rescue treatment

On rescue treatment, we acknowledge the consideration of the Appraisal Committee that monitoring and provision of rescue treatment such as intravenous immunoglobulin is largely symptom dependent and may only be required infrequently.

The extent of rescue medication used in our economic model was taken directly from that observed in our two phase 3 trials. In the absence of a more robust alternative data source on rescue medication use, the extent of use observed in our trials was considered to be the most appropriate source of data to use in our economic model. Furthermore, it is also the case that the clinical outcome in terms of experience of bleeds used in our economic model reflects the extent of use of rescue medication observed in the trials. Had less rescue medication been used in our trials, it is reasonable to suppose that the clinical outcome for patients in the placebo arm would have been worse and the incremental improvement in clinical outcome with romiplostim would

have been greater. It may be the case that less rescue medication could be used in patients in clinical practice than in the trials, leading to a lower cost offset (i.e. savings from rescue medications avoided) and higher ICERs for romiplostim. Equally it may be the case that the advantage in clinical outcome from use of romiplostim in clinical practice would be greater than estimated in our economic model, leading to lower ICERs for romiplostim. It is impossible to quantify the net impact of these two effects (savings from rescue medications avoided vs. advantage in clinical outcome from use of romiplostim) and, therefore, a robust economic analysis should be based on data which links the extent of rescue medication used with the associated clinical outcome; in this case, the data from our clinical trials.

In terms of rescue medication, the ACD states that *"the proportion of patients assumed in the model was approximately 70%, of whom approximately 60% required intravenous immunoglobulin"* implying that 42% of patients in the model required IVIG per cycle. We believe that this may not represent the proportions of IVIG assumed in the model as it differed between the splenectomised and non-splenectomised groups with the latter group requiring 20% IVIG and the former group requiring 40% IVIG every cycle. The ACD describes that the provision of rescue treatment is largely symptom dependent and may only be required infrequently. We are of the view that the 'more refractory' nature of the patient population included in the romiplostim trials explains the 'higher' levels of rescue medication observed compared with the perhaps more conservative treatment of less severe chronic ITP patients in clinical practice (indeed the licence for romiplostim is as a second-line treatment in non-splenectomised patients where surgery is contraindicated and in splenectomised patients who are refractory to other treatments[7]). Further, the recent (July 2009) withdrawal of the availability of all market authorisations for anti-D immunoglobulin leaves one less treatment option with respect to rescue medication and could result in the increased use of IVIG in clinical practice[13].

In summary, we believe that the chronic refractory patients with severe ITP and high risk of bleeding are the ones likely to use rescue medications to the extent observed in our trials and beyond. It is also in this group of patients that ITP is a life threatening disease where limited therapeutic alternatives are available and where the need for effective treatments is highest.

5. Conclusion

The Appraisal Committee noted that several assumptions in our base case resulted in the underestimation of the cost per QALY gained. We trust that the analyses we have presented in this response will provide the Appraisal Committee with sufficient reassurance that the cost-effectiveness case for romiplostim is sufficiently robust.

ACD Section 4.13

"In summary, the Committee considered that, in current UK practice, treatment with romiplostim would be prescribed only for people with chronic ITP who have symptoms or a risk of bleeding severe enough to warrant intervention, and therefore the appropriate comparator pathways are those starting with active treatment rather than 'watch and rescue'."

"The Committee also noted that significant wastage of vial contents would occur in practice and therefore the drug cost of romiplostim would be substantially higher than that proposed in the manufacturer's submission."

"The Committee also concluded that several assumptions in the manufacturer's base case resulted in underestimation of the cost per QALY gained. These included: the cost of comparator treatments; cost of blood film assessment; and the use of EQ-5D utility values other than from the RCTs to model health-related quality of life. The Committee therefore concluded that it could not recommend romiplostim for the treatment of people with chronic ITP as a cost-effective use of NHS resources."

We agree with the Appraisal Committee that in practice, treatment with romiplostim would be prescribed only for people who have symptoms or are at high risk of bleeding. It is in this group of patients that ITP is a life threatening disease where limited therapeutic alternatives are available and where the need for effective treatments is highest. In fact, the SMC is its recent advice on romiplostim[14] (12th October 2009) recommended its use in this group of patients within its licensed indication. *"Romiplostim is restricted to use in patients with severe symptomatic ITP or patients with a high risk of bleeding."*

A key issue to consider is the safety concerns around existing unlicensed treatments for ITP, such as rituximab, whose long term effects have not been assessed in well-conducted RCTs. Indeed, a recent publication[6] demonstrated the increased risk of progressive multifocal leukoencephalopathy (PML), a rare disease of central nervous system that results from reactivation of latent JC polyoma virus (JCV) after treatment with rituximab. It found that 57 patients, including 1 ITP patient, developed PML after treatment with rituximab. Further, immunosuppressants used to treat ITP patients have the potential to cause severe, possibly life-

threatening, immunosuppression[4]. It is noteworthy that a treatment like romiplostim is not immunosuppressive, has undergone rigorous RCTs, and has demonstrated high efficacy[4].

We understand the concerns of the Appraisal Committee that the drug cost of romiplostim could be higher than that proposed in our submission and that the average dose that would be used in clinical practice is unknown. In our revised base case, we have demonstrated with patient level data that the average (mean) number of whole vials required by an average patient is between 0.99–1.04 (more realistic versus conservative approach) 250mcg vials per non-splenectomised patient and between 1.39–1.49 (more realistic versus conservative approach) 250mcg vials per splenectomised patient (assuming 100mcg vial is available, assuming no overfill, allowing for wastage and adjusting for patients dosed above the maximum dose stated in the SPC). We expect the average number of vials required (and the average dose) based on the trial to be an overestimate of that likely to be observed in UK clinical practice for the following reasons:

- The clinical trial was powered to demonstrate a platelet response of between $50x10^9$/l and $200x10^9$/l. The ERG report notes that, *"The analysis however primarily considers evidence where the cut-off for treatment is <50 x10^9/l; higher than would typically be used in practice in the UK."* If this were the case in clinical practice in the UK, it would likely mean that a lower dose would be required than observed in the clinical trials.

- The average number of vials was calculated from our trial data, using weekly doses from week 13 to end of the study at week 24, and excluding the initial titration period. This is a conservative approach as the exclusion of lower doses during the titration period will have increased the average dose (and number of vials required) of romiplostim per patient.

- The dose calculations strictly assumed that patients requiring any amount larger than 250mcg, and larger than 100mcg, would receive additional vials. In practice, one would anticipate that a patient requiring 260mcg would be dosed with one 250mcg vial or a patient requiring 110mcg would be dosed with one 100mcg vial making it reasonable to assume a 5%-10% 'underdose' in clinical practice. Therefore the average number of vials calculated for the economic could be an overestimate compared to what might happen in clinical practice.

- The World Health Organisation approved Daily Defined Dose for romiplostim stipulates a daily dose of 30mcg[15]. This equates to a weekly dose of 210mcg, which is smaller than that observed in the trials (dose observed in the trials is estimated to be between 247mcg-260mcg based on 0.99–1.04 250mcg vials per non-splenectomised patient and between 347mcg-373mcg based on 1.39–1.49 250mcg vials per splenectomised patient) and suggests that doses in clinical practice could be lower.

We trust that the analyses we have presented on the key drivers of the economics will provide the Appraisal Committee with significant reassurance that the ICERs for romiplostim are sufficiently robust. The revised base case ICERs of between £21,306–£25,951 in the non-

splenectomised group and £13,951–£31,060 in the splenectomised group, demonstrates that romiplostim is a cost-effective treatment. We would like to request that NICE recommend its use in chronic ITP patients where active therapy is warranted, i.e. in patients with severe symptoms or at high risk of bleeding.

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