**RESPONSE TO THE EVALUATION REPORT ON ROMIPLOSTIM**
**Confidential information is redacted**

We have reviewed the Evaluation Report and the analyses undertaken by the Evidence Review Group (ERG) for the appraisal of romiplostim for the treatment of adults with chronic idiopathic (immune) thrombocytopenia purpura (ITP). We welcome the opportunity to respond to the ERG Report, and in our response, we address key issues highlighted in the ERG Report that we have not already addressed in our response to the ACD.

1. **ERG Report, Summary Page IV and Clinical Effectiveness Page 58**
*"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."*

*"No criteria set for patients' baseline platelet counts (should be ≤ 30 x 10$^9$/l unless the patient experienced bleeding or was being prepared for surgery)"*

Our Phase III randomized controlled trials (RCTs) were designed in collaboration with regulatory authorities, and a platelet count ≥50x10$^9$/l was considered to be the appropriate and ethical level in a clinical trial setting to completely mitigate the risk of a bleeding event[1]. Whilst a platelet count of ≥50x10$^9$/l was the target in the clinical trials, the romiplostim trials enrolled patients with a pre-treatment platelet count of <30x10$^9$/l. Indeed, the baseline characteristics of patients in the clinical trials show that patients were relatively refractory with a mean platelet level of below 20x10$^9$/l.

The literature review of efficacy data for comparators identified a platelet count ≥50x10$^9$/l as the most commonly reported efficacy endpoint. We were not able to obtain efficacy for all comparators using a target platelet level of ≥30x10$^9$/l. Further we were not able to restrict inclusion to studies of patients with a baseline platelet count <30x10$^9$/l, as only a small number of studies met this criterion. As such, any potential bias here is likely to be against romiplostim, since the romiplostim trials only included patients with a baseline platelet count <30x10$^9$/l.

Our response to clarification question A2 included a hypothetical scenario using an efficacy threshold of ≥30x10$^9$/l platelets. The results of this analysis showed that the effect on ICERs was negligible. In this scenario, we were able to estimate revised overall response rates for romiplostim but not for the comparators; the response rates for patients achieving a overall platelet response of ≥30x10$^9$/l was ▉▉▉ higher versus that reported for the threshold of ≥50x10$^9$/l. We therefore conservatively adjusted the efficacy estimates upwards for the comparators by increasing the response rate by 10%. We believe that this approach was also conservative on both the dose and cost as it conservatively assumed that the romiplostim dose

required to maintain a target level of $\geq 50 \times 10^9$/l would also be required for a lower target level $\geq 30 \times 10^9$/l.

## 2. ERG Report, Clinical Effectiveness Page 24 & 25

*"Simply pooling of effect sizes as has been done by the manufacturer has the potential of producing biased and unreliable estimates. Weighting by sample size also has the potential for large studies of low quality to dominate the pooled estimates. In effect the manufacturer conducted an analysis similar to a fixed effect meta-analysis, the implicit assumption of which is that the true effect does not differ between studies. No attempt was made to assess evidence of heterogeneity in the analysis although the heterogeneous nature of the included studies is apparent. An estimate of the between study variance could have been used to modify the weights used to calculate the summary estimates."*

*"Previous research has compared the results obtained from pooling observational data and RCT data. This research suggested that, compared with the pooled RCT data, pooling observational data may lead to biased estimates (of perhaps as much as 30% to 100% of the relative effect size) either for or against the experimental treatment (in this case romiplostim)."*

In the absence of a common comparator arm in the available studies to appropriately link treatments and conduct a Bayesian mixed treatment comparison, the best alternative was to calculate the platelet response rates separately for romiplostim and for each of the comparators. We note that the ERG considered this and *"the ERG acknowledged that pooling using formal methods may have also been inappropriate."* Therefore, the method of using a weighted average (weighted by number of patients) to derive a pooled estimate of efficacy was employed as this took into account the variability in efficacy observed in the individual studies and was therefore considered to provide the most robust estimate of efficacy. Indeed, alternative methods such as using the median which ignores study variability were considered, but an approach using the average (which takes variability into account) rather than the median was considered more robust.

We acknowledge that observational studies may overestimate effect sizes, and this was noted in our original submission. However, only observational data was available for the majority of the comparator treatments. We therefore agree with the ERG that *"an alternative method of analysis might perhaps have yielded no significant differences from that contained in the submission."* Indeed, we believe that any bias was likely to favour the comparator treatments over romiplostim and bias the ICERs upwards because romiplostim was assessed within RCTs recruiting patients with severe ITP, whereas the comparators were mainly assessed within uncontrolled case series recruiting patients with ITP of varying severity. In order to understand

the bias and simplify the case, we focus our attention on the comparison between romiplostim and rituximab (an unlicensed treatment for ITP). The direction of bias in terms of level of evidence, duration of ITP and baseline platelet count is summarised below:

- Both Arnold 2007[2] and Zhou 2008[3] systematic reviews were based on rituximab use in uncontrolled single-arm studies and defined response rates as ≥50x10$^9$/l at any point in time whereas romiplostim response data were taken from randomised controlled trials with stricter response rate criteria of ≥50x10$^9$/l for at least 4 weeks[4]. Efficacy data taken from unblinded, uncontrolled studies could overestimate effect sizes by up to 20%[5,6] biasing effectiveness in favour of rituximab.

- Patients in the romiplostim arm of our phase 3 trials had a mean duration of ITP of ███ ███ in non-splenectomy group and ███ in the splenectomy group. Arnold 2007[2] reported mean duration of 51 months for patients (of which half were splenectomised) in the rituximab studies. It can be inferred that splenectomised patients in the romiplostim studies were more severe than patients in the rituximab studies in terms of ITP duration as they had a longer duration of ITP. Cooper 2004[7] showed that longer duration of ITP was associated with a poor response. As such, it is reasonable to postulate that any bias (due to differing ITP duration) in the indirect comparison of response rates is likely to favour rituximab.

- Patients in romiplostim studies[4] had a median baseline platelet count of 19x10$^9$/l in non-splenectomised and 14x10$^9$/l in splenectomised groups respectively with a range of (2-29)x10$^9$/l. Arnold 2007[2] reported that the range of platelet counts was (1-89)x10$^9$/l for the studies included in their review. The platelet count range for rituximab includes counts above 30x10$^9$/l, i.e. less severe patients. Godeau 1997[8] and Damodar 2005[9] found significantly lower mean baseline platelet count in non-responders in their studies. As such, it reasonable to postulate that any bias (due to differing baseline platelet count) in the indirect comparison of response rates is likely to favour rituximab.

### 3. ERG Report, Additional Work Undertaken, Page 97, 98 & 100

*"The results of the cost-effectiveness analysis are based on the indirect comparison of observational data. Such comparison may overestimate or underestimate the relative effectiveness of romiplostim. In this sensitivity analysis the ERG considers the implications when the data within the economic model overestimates the effectiveness of romiplostim. In these sensitivity analysis the proportion of people responding to romiplostim and the duration of response are reduced to 75% and 25% of the values used in the base case analysis."*

We acknowledge that observational studies may overestimate effect sizes, and this was noted in our original submission. Unlike romiplostim, studies for the majority of the comparator treatments were mainly uncontrolled case series. Indeed, we believe that any bias was likely to favour the comparator treatments over romiplostim and bias the ICERs upwards because romiplostim was assessed within RCTs recruiting patients with severe ITP, whereas the comparators were assessed within observational studies recruiting patients with ITP of varying severity.

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[10]."* The recent International Consensus Report on the Investigation and Management of Primary Immune Thrombocytopenia[11] 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 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.

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. Likewise, we consider it inappropriate to perform a sensitivity analysis by reducing only the efficacy of romiplostim significantly (i.e. reduced to 25% of the values used in the base case analysis) and leaving comparator effectiveness unchanged when it is the comparators that have limited and poor quality data. A more appropriate sensitivity analysis would have been to reduce the efficacy of

the comparators (with their limited evidence base) and leave the efficacy of romiplostim unchanged, due to the relative high quality of our clinical trial data as noted in both the CHMP assessment report and the International Consensus Report[10,11].

We performed a sensitivity analysis where the proportion of people responding to the comparators and the duration of response are reduced to 25% of the values used in the base case analysis. This resulted in a decrease in the ICERs, from £25,951 in our revised conservative base case to £19,464 in this sensitivity analysis in the non-splenectomised group and from £31,060 in our revised conservative base case to £18,097 in this sensitivity analysis in the splenectomised group. The ICERs decrease further from £21,306 in our revised realistic alternative base case to £15,247 in this sensitivity analysis in the non-splenectomised group and from £13,951 in our revised realistic alternative base case to £2,737 in this sensitivity analysis in the splenectomised group.

**References**

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