Celgene Ltd.
Morgan House, Madeira Walk
Windsor
SL4 1EP
United Kingdom

[redacted]

[redacted]
National Institute for Health and Clinical Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BD

Dear [redacted]

Bortezomib and Thalidomide for the first-line treatment of multiple myeloma
Celgene Comments on Assessment Report

Thank you for the opportunity to comment on this Assessment Report. We have concentrated our comments about the Southampton Technology Assessments Centre (SHTAC) economic modeling. The table below provides relevant section numbers or states "general" where an observation made relates to the report as a whole rather than one specific section.

Should you have any questions, please do not hesitate to contact us.

Yours Sincerely

[redacted]

Section Number	Comment
General	We note that the SHTAC model does not consider or adjust for cross-over therapy. This is surprising given that robust methods are available and well-documented from the STA of lenalidomide.
1.14.3.5	Dosing for the comparative therapies was based upon clinical trial data and physician opinion. There was no accounting for dose reductions in the SHTAC model. Thalidomide dosing was in line with standard clinical practice but was below what was used in the trial. The model likely represents the average dose used in the real world. Bortezomib dosing is slightly more complex as the weight based dosing allows for the potential for vial sharing. The SHTAC model assumed that no vial sharing exists which represents a slightly conservative approach. While vial sharing has potential to create cost savings, further information as to its feasibility in the real world should be collected.
1.14.3.5	Concomitant medications in addition to the MP were assumed to be the same across therapies (no additional costs added) except that DVT

	prophylaxis (dalteparin 5000 units daily) was added to all patients managed with thalidomide. This is the most expensive prophylaxis treatment option for DVT and thus the most conservative approach.
1.14.2	The model allowed for patients who fail/discontinue therapy to begin second line treatment. As very little data exist to inform either efficacy (response and survival) or HRQoL, the model only includes second line treatment as a cost. Including costs alone unfairly punishes the more expensive treatment arm as it becomes a tariff without benefit.
1.14.2	More clarity on baseline characteristics would be helpful. Little information is currently available except that patients not eligible for stem cell transplant are modeled, similar to the patient populations in the considered trials.
Table 1.14.3.2	By using empirical survival data directly, the SHTAC model provided a closer fit to the trial data than using parametric distributions (e.g. Weibull). However, the following problems were identified: 1. By reading the survival point data from Kaplan-Meier plot,s censoring information is not used. So estimates of hazard ratios are not as accurate as those obtained through patient-level data analysis. 2. The effect of cross-over is not considered. 3. The model may fail to accurately predict the survival beyond trial period by simply using the average hazard rates and hazard ratios (HRs) during the trial period, especially given that more than 45% patients are still alive after trial period. 4. The model did not adjust HRs based on trial population characteristics - the SHTAC model assumes the patient population is similar across the 5 selected trials.
1.14.3.4	Utility values were not adjusted for adverse events (AEs), but lower utility values were assumed for the duration of therapy. It is assumed that these lower values take into account AEs related to treatment, but this approach does not differentiate across types of AEs and 'punishes' therapies which may be better tolerated, *i.e.*, where patients can remain longer on treatment.
1.13	The Celgene thalidomide model used a thalidomide-specific survey and similar methods as the costing analysis carried out for the lenalidomide submission. Contrary to the assessment report's summary, Celgene did include outpatient consultation costs in its calculations (see table 5.5 in the Celgene submission).
General	We believe that with only very minor misunderstanding of the Celgene submission, SHTAC conducted a fair review of the thalidomide model and their model represents a fair interpretation of the VMP trial data.