

[REDACTED]

9 March 2012

**RE: Single Technology Appraisal – Vemurafenib for the treatment of locally advanced or metastatic, BRAFV600 mutation positive malignant melanoma**

[REDACTED]

Our response to the clarification questions is provided below. If any further clarification is required we would be more than happy to provide it.

[REDACTED]



[REDACTED]

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## **Section A: General requests**

- A1. Priority request:** Please provide a copy of the full Clinical Study Report and all of its appendices as soon as possible.

Please see the attached. The CSR, its contents, and any subsequent analyses performed on its content, are to be regarded as commercial in confidence.

- A2. Priority request:** Please provide a copy of the European public assessment report (EPAR). If this document is not yet available, please could you confirm when it will become available, and provide a copy to NICE at this point.

An EPAR is not currently available. It is anticipated that this will become available in the second quarter of 2012.

## **Section B: Clarification on the clinical effectiveness data:**

- B1.** Please provide a full description of all protocol violations in the BRIM3 trial including the number and type of violations for each arm for the whole trial population.

One BRAF V600E mutation negative patient was randomized in error (received 1 infusion of dacarbazine).

One patient aged 17yr and 9 months was randomised on 8 October 2010. This was approved upfront by the Central Ethics Committee on 29 Sep 2010.

- B2.** Please provide an explanation for the uneven split of the significance level across the two primary outcomes (that is, why was  $\alpha=0.045$  for overall survival and 0.005 for progression free survival?).

The type 1 error for the study was 0.05 two-sided. Because there were 2 co-primary efficacy endpoints, the type 1 error needs to be allocated across the two endpoints so that overall type 1 error is maintained at 0.05 two-sided. This was accomplished for this study by allocating 0.045 for the OS endpoint and 0.005 for the PFS endpoint.

- B3.** Section 4.1.2, page 127 of the statistical analysis plan (supplementary material to NEJM Chapman publication) states 'if, in addition to the single planned interim efficacy analysis, any unplanned interim analyses of OS are performed, a nominal 0.00001 statistical penalty will be applied to the threshold for statistical significance for the OS endpoint'. The manufacturer's submission notes two additional sets of analyses were performed (March 2011 and October 2011), as well as the pre-specified interim analysis (December 2010). Please provide the following information:

1. What analyses were performed at these time points and if any efficacy analyses were performed, what significance level was chosen.

The statement "*If, in addition to the single planned interim efficacy analysis, any unplanned interim analyses of OS are performed, a nominal 0.00001 statistical penalty will be applied to the threshold for statistical significance for the OS endpoint*" referred to any unplanned interim efficacy analyses that may have taken place before the OS interim analysis that was planned to take place with 50% information. There were no such unplanned analyses performed before the OS interim analysis that was planned to be performed with 50% information.

The analyses that were performed (March 2011 and October 2011) were performed after statistical significance of the OS benefit was demonstrated (from the analysis based on the December 2010 clinical cut-off date). The final PFS analysis occurred at the time of the OS interim analysis. The March 2011 and October 2011 OS analyses were not pre-planned per the protocol; instead we performed those analyses for informational purposes upon health authority request. Because these analyses were not pre-planned per the protocol, and these analyses occurred after statistical significance of the OS endpoint was already established based on the December 2010 cut-off, these analyses did not involve formal hypothesis testing and therefore a significance level was not applicable to those analyses. For the March 2011 analysis, PFS, OS and safety were updated; for the October 2011 analyses, OS was updated.

2. Whether the additional analyses were pre-specified and if so, can you please explain why they were not detailed in the statistical analysis plan?

See response to question 1 above.

3. Can you please provide a rationale for performing these analyses and confirm if the data safety monitoring board were informed that these additional analyses were taking place.

See response to question 1 above. Per the data safety monitoring board (DSMB) charter, the DSMB reviewed the efficacy interim analysis results (December 2010 cut-off) which involved formal hypothesis testing for OS and PFS, and the DSMB recommended release of those results based on compelling efficacy. Those results established the statistical significance of the treatment benefit on OS and PFS. The DSMB was informed of the results of the updated analyses (March 2011 and October 2011) that were performed based upon health authority requests.

4. Confirm when the final analysis will take place and clarify how it will be adjusted to take into account these additional analyses. Please also indicate whether the statistical analysis plan will be updated to state that these analyses have been performed post-hoc.

As stated above, formal hypothesis testing for OS and PFS was performed at the time of the OS interim analysis (December 2010 cut-off); because the OS interim analysis boundary was crossed, the statistical significance of the treatment benefit on OS was established at the OS interim analysis. Because the OS interim analysis boundary was crossed, no additional formal hypothesis testing will occur. Because no additional hypothesis testing will occur, no modifications will be made to the SAP.

- B4.** Page 73 of the submission states 'with considerable numbers of patients being followed up, the data set is still immature and subsequent analyses of further data-cuts are expected'. Please can you:

- Confirm how many subsequent analyses you expect to perform and the rationale for not waiting until the end of follow-up.
- Clarify what these additional analyses will entail and how the final analysis will be determined.

- Explain why these possible additional analyses are not detailed in the statistical analysis plan.

As stated above, formal hypothesis testing for OS occurred at the time of the OS interim analysis and statistical significance of the OS benefit was established at the OS interim analysis. Subsequent updated analyses of OS are performed upon health authority request. An OS updated has been requested as part of marketing approval in the EU, and that update is due May 31, 2012.

It should be noted that the statement that the data set is 'immature' was made from the perspective of an economic modeller attempting to quantify the *precise* magnitude of benefit offered by vemurafenib rather than from a regulatory perspective.

### **Section C: Clarification on the cost effectiveness data:**

**C1. Priority request:** The ERG believes the presented clinical results do not allow for exploration of issues related to time-to-events. Therefore, the ERG would like to request the following additional results in the format of Product-Limit Survival tables (that is, using SAS LIFETEST procedure, an example is included at the end of this document) showing for each event time:

- Time-to-event from baseline (days)
- Product-limit estimate of survival proportion
- Standard error of survival proportion
- Number of patients failed
- Number of patients remaining at risk

Please provide the following analyses also in the format of Product-Limit Survival tables:

- A progression free survival from the October 2011 cut of the BRIM3 trial data for progression free survival by trial arms (vemurafenib and dacarbazine).

As stated on page 144 of our submission PFS data is not available from this cut-off date. The October cut was taken upon a request from the EMA for more mature overall survival data and so a cut of the data was made and overall survival assessed. Data for anything else of interest from this cut-off (PFS, dosing, response rates etc) is not available.

- Post-progression survival from the date of non-fatal disease progression by trial arm [vemurafenib and dacarbazine], with dacarbazine patients data censored at the date of cross-over to vemurafenib, using the October 2011 cut of the BRIM3 trial data.

Post-progression survival cannot be estimated without PFS. As stated in our submission this data is not available.

**C2.** Please provide an updated version of the consort diagram on page 69 (Figure 6) for the October 2011 cut of the BRIM3 trial data.

As stated on page 144 of our submission only OS data is available from the October 2011 cut-off. It is therefore not possible to produce a consort diagram for the October 2011 cut-off.

- C3. Priority request:** Please provide the following for the vemurafenib treatment arm only:
- Define two mutually exclusive subgroups of patients: those who continued on treatment until disease progression, death or censoring; those who discontinued treatment prior to disease progression, death or censoring.
  - Based on the above definitions, please construct a Kaplan-Meier curve comparing these two subgroups in terms of progression free survival and overall survival using the October 2011 cut of the BRIM3 trial data.

As stated in our submission PFS and dosing data is not available from the October 2011 cut.