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National Institute for Health and Clinical Excellence

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[redacted]

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

The Evidence Review Group (Liverpool Reviews & Implementation Group) and the technical team at NICE have now had an opportunity to take a look at the submission received on the 1st February 2012 by Roche. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost-effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **17:00, 9th March 2012**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

[redacted]

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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.

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.

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.

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

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:

- What analyses were performed at these time points and if any efficacy analyses were performed, what significance level was chosen.
- Whether the additional analyses were pre-specified and if so, can you please explain why they were not detailed in the statistical analysis plan?
- 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.
- 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.

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.

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).
- 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.

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.

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.

Example of output (SAS) required from analyses specified in C1

The LIFETEST Procedure

Product-Limit Survival Estimates						
SURVIVAL		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		0.8548	0.1452	0.0447	9	53
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0