[redacted]
Health Economics and Strategic Pricing Director

8th August 2011

[redacted]
Chair, Appeal Committee
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London WC1V 6NA

RE: LAPATINIB OR TRASTUZUMAB IN COMBINATION WITH AN AROMATASE INHIBITOR FOR THE FIRST-LINE TREATMENT OF METASTATIC HORMONE-RECEPTOR POSITIVE BREAST CANCER THAT OVER EXPRESSES HER2

Dear [redacted],

Thank you for your letter dated 25 July 2011, confirming that Roche's appeal will be considered at an oral hearing before NICE's Appeal Panel.

In your letter you set out your preliminary views in relation to the appeal advanced by Roche in our appeal letter of 15 July. We now provide our further comments and clarification in response to the matters raised in your letter, in advance of your final decision on the admissibility of our points of appeal.

We hope that we have addressed the matters set out in your letter, although if you have further queries, we will be pleased to provide additional clarification. We look forward to receiving your response to this letter and your final decision in relation to the admissibility of our appeal.

Yours Sincerely,

[redacted]
Health Economics and Strategic Pricing Director

Ground 1

<u>Point 1.1</u> The Appraisal Committee's conclusions in relation to (a) the life expectancy of people eligible for trastuzumab in combination with an aromatase inhibitor for first line treatment of metastatic hormone receptor positive breast cancer that over expresses HER2 and (b) the survival gain associated with trastuzumab therapy, are not stated and it is unclear whether the Committee concluded that these criteria for the 'End of Life' advice were met.

Noted and accepted.

<u>Point 1.2</u> The lack of guidance issued by the Institute in relation to the calculation of small patient populations for the purposes of the End of Life advice is unfair

In your letter, you express the preliminary view that this point of appeal is not admissible. Your reasons for this conclusions appear to be: (a) you say that the Appeal Panel in TA 227 did not recommend that further guidance be issued in relation to the calculation of small patient populations for the purposes of the end of life criteria, but simply that NICE should consider whether such guidance should be issued; (b) the Institute would in any event have had no opportunity to act on the recommendation of the Appeal Panel in TA 227 for the purposes of the Appraisal Committee's consideration of this appraisal, in view of the timing of the appeal decision in that case; and (c) you say that the Appraisal Committee cannot be criticised for failing to take into account guidance which has not and may never be issued.

As a preliminary matter and by way of clarification, Roche does not suggest that the Appraisal Committee in this case should have taken into account guidance issued by the Institute as a consequence of the decision in TA 227. Our point of appeal is that the decision in TA 227 provides support for our case that such guidance should have been issued, as a matter of procedural fairness, to assist Appraisal Committees in assessing whether technologies qualify for consideration under the end of life criteria.

We respond to the specific matters identified in your letter, below:

(a) The conclusion of the Appeal Panel in TA 227

During the course of the appeal hearing in relation to TA 227, it became clear that different Appraisal Committees had been interpreting the "small patient population" criterion inconsistently and the Appeal Panel therefore suggested that the Institute might wish to consider issuing guidance to assist Committees in relation to this issue. While the Appeal Panel did not direct the Institute to issue guidance (it does not have power to issue such a direction), it is clear from the wording of the appeal decision that the Panel regarded the fact that different Committees had adopted different approaches to this issue as unsatisfactory.

In relation to the lack of fairness to consultees, as a result of the absence of guidance from the Institute, we respectfully submit that the decision of the Appeal Panel in TA 227 should not be followed. It cannot be fair that different Appraisal Committees adopt different approaches to the way in which the size of the relevant patient population is calculated, so

that the outcome of an appraisal may be determined simply by the fact that one Appraisal Committee is allocated to consider an appraisal rather than another. The fact that an Appraisal Committee has spent time considering an issue is of course wholly irrelevant to the question of whether the procedure followed by the Committee was fair.

While you may be guided by the decisions of earlier Appeal Panels, you are not bound by them (paragraph 4.4.4 Guide to the Technology Appraisal Appeal Process). Accordingly, we believe that the conclusions of the Appeal Panel in TA 227 should not determine the outcome of this appeal, particularly in view of the factual differences between the two appraisals. In particular, it is unclear to what extent the Appeal Panel which considered TA 227 was influenced in its conclusions on fairness by the fact that even if the technology in that case had been found to satisfy the small patient population criterion, it had been found to be ineligible for the end of life guidance on other grounds.

Finally, the Appeal Panel in TA 227 did not, in reaching its decision, address the fact that approaching the calculation of the small patient population on the basis of the number of patients eligible in accordance with the licensed indication (interpreted broadly, without consideration of those patients who are clinically ineligible for treatment as a result of matters listed under precautions, warnings and side effects) is inconsistent with the Institute's stated purpose in limiting the end of life guidance to technologies used to treat small numbers of patients, where the manufacturer's ability to recover development costs is limited.

Accordingly, the fact that an Appeal Panel has considered some of the related issues in the context of a different appraisal does not preclude the point raised by Roche being fully addressed in relation to trastuzumab.

(b) The decision of the Appeal Panel in TA 227 was issued too late

There are many examples of appraisals where guidance has been delayed as a result of developments even after a FAD has been prepared, but before it has been circulated to consultees. While it is the case that the decision of the Appeal Panel in TA 227 was published immediately after the FAD in this appraisal was issued, the content of the decision was clearly known to NICE and it would have been possible for the Appraisal Committee or the Institute itself to have directed that the FAD should be delayed while consideration was given to whether guidance would be produced as described by the Appeal Panel.

(c) The uncertainty as to whether the Institute will decide to issue guidance

Roche accepts that it is possible NICE will decide not to issue guidance in relation to the approach to be followed by Appraisal Committees when calculating the size of the patient population for a particular health technology, although it believes that the lack of such guidance is unfair. However in this case, the Appraisal Committee did not seek guidance either during the course of the appraisal or when the decision of the Appeal Panel in TA 227 was issued.

Ground 2

<u>Point 2.1</u> The Appraisal Committee's addition of a further 2,000 patients to the 7,000 population figure estimated by Roche for trastuzumab equates to double counting of patients. These calculations suggest that nearly twice as many mBC patients are potentially eligible for trastuzumab as there are HER2+ mBC patients in the UK. This cannot be reasonably justified in light of the evidence presented and is not a sound a suitable basis for the issuance of guidance to the NHS.

Noted and accepted.

<u>Point 2.2</u> The Appraisal Committee's statement regarding the overall survival of patients who received aromatase therapy monotherapy in the TAnDEM trial failed to allow for patient cross over

Noted and accepted.

<u>Point 2.3</u> The Appraisal Committee's statements regarding the overall survival benefit associated with trastuzumab therapy are unreasonable in light of the totality of the data presented

Noted and accepted.

<u>Point 2.4</u> The conclusion by the Appraisal Committee that estimates of progression free survival for the aromatase inhibitor monotherapy in the TAnDEM trial were likely to be too low disregards the fact that the patient population in TAnDEM was different from that in EGF30008

In your letter, you say that, while you agree this is a valid appeal point, you believe the Appeal Panel may benefit from further elaboration. We provide the following summary to assist the Panel, although this is intended to supplement the case made in our appeal letter and not to replace those submissions.

In considering this appraisal the Appraisal Committee considered (a) a trial comparing lapatinib in combination with an aromatase inhibitor (AI) compared with AI monotherapy (the EGF30008 trial); and (b) a trial comparing trastuzumab in combination with an AI compared with AI monotherapy (the TAnDEM) trial.

The Appraisal Committee noted the differences in progression free survival (PFS) between participants in the EGF30008 trial and participants in the TAnDEM trial and stated that clinical specialists had indicated that PFS in the comparator group in the EGF30008 trial more closely reflected that seen in UK clinical practice (paragraph 4.3.4 of the FAD). As a consequence of its conclusion that PFS in the comparator group in TAnDEM was shorter than that generally seen in UK clinical practice, the Committee suggested that the estimates from TAnDEM were

likely to under-estimate PFS in patients receiving AI monotherapy (paragraph 4.3.12 of the FAD). The Committee therefore concluded that Roche's estimate of the ICER for trastuzumab "*was too low given that people in the aromatase inhibitor group appeared to progress much quicker than would be expected in clinical practice*" (paragraph 4.3.14 of the FAD).

However in reaching this conclusion, the Appraisal Committee did not take account of the fact that the patient population recruited into TAnDEM was generally different from that recruited into EGF30008 and comprised patients who had a worse prognosis. This situation affected the PFS seen in both the trastuzumab and the comparator groups; however the conclusion of the Appraisal Committee in relation to the data from the AI group disregards the nature of the patient population who participated in the trial and the randomisation process and is therefore unreasonable.

The effect of this approach by the Appraisal Committee is that it incorrectly concluded that the benefits of trastuzumab were less than those demonstrated by the TAnDEM trial and therefore that the ICER was higher than is in fact the case. In fact, if the economic model was revised to take into account a better prognostic population (such as that in EGF30008), and therefore an improved absolute benefit of trastuzumab, the ICERs would be lower than those presented to the Committee – not higher.