[redacted]

BY EMAIL

03 October 2012

RE: Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of ovarian cancer

[redacted]

Please find below our response to the clarification question from the ERG and the technical team at NICE received 19th September 2012. I would also like to advise you that our response contains no commercial or academic in confidence material and the confidential information checklist provided previously should be considered applicable here.

We hope this feedback helps clarify the issues raised by the ERG and the technical team at NICE. If you require any further clarification or information then please do not hesitate to contact us.

Yours Sincerely,

[redacted]

Section A: Clarification on effectiveness data

A1. **The primary outcome measure in Study GOG-0218 is PFS based on investigator assessment, please clarify whether this is censored for CA-125 or without censoring.**

The FDA requested a primary PFS efficacy endpoint in GOG-0218 based on investigator assessment, censored for CA-125 – only progressions. Any patient who progressed solely on the basis of rising serum CA-125 levels was censored at the time of last radiographic assessment during which the patient was known to be progression free. These are the primary data quoted in the Roche/Genentech Clinical Study report for GOG-0218.

A2. **The primary analysis of PFS in Study GOG-0218 in the EMA/CHMP Assessment report is without censoring and the primary analysis in the manufacturer's submission appears to be censored. Please explain why different results are used.**

As stated above in A1, the primary analysis of investigator-assessed PFS was censored for CA-125. However, the GOG per-protocol analysis was not censored for CA-125. The CHMP requested both these datasets and these are recorded in the Avastin SmPC and the Assessment report.

A3. **Please clarify what is meant by final analysis (September 2010, page 79), primary analysis (page 80) and updated analysis (August 2011, page 81) and why there is inconsistency in reporting with different time points for different assessments. For example:**

For the primary study outcome of PFS the "primary" analysis was at the protocol-specified time for the "final" PFS analysis (September 2010). PFS was analysed at this time, as were the secondary and exploratory endpoints, including an interim OS analysis.

An updated analysis was conducted on a data cut-off of August 2011, mainly to provide a more complete dataset for OS, with more mature data. There was also an updated analysis of PFS at this time point.

- **for the PFS results of the GOG-0218 study, the investigator assessment, censored data has a final analysis date of September 2010 (Table 10, page 80) and updated analysis without censoring date of August 2011 (page 82); however, there do not appear to be updated censored data**

The updated PFS analysis did not report data censored for patients defined as progressing solely by a rising CA-125. This data is not available.

- **there do not appear to be updated PFS IRC results**

In GOG-0218 the IRC assessment of PFS was an exploratory analysis, to confirm the validity of investigator assessed PFS. This IRC analysis was conducted at the time of the primary PFS analysis (data from September 2010). Although PFS was updated at a later time, no secondary or exploratory endpoints, with the exception of OS, were re-evaluated.

- **OS updated results are not reported (although they are reported in the NEJM trial publication)**

The most recent OS data were reported in the submission for both GOG-0218 (Table 15, page 85) and ICON7 (Table 21, page 94). For clarity, results for each of the OS analyses conducted are repeated below in Table 1 and Table 2.

Table 1: Overall survival analyses in GOG-0218

Interim OS analysis, data cut-off February 5th 2010 (ITT)			
	CPP (n= 625)	**CPB15 (n= 625)**	**CPB15+ (n= 623)**
Median OS (months)	39.3	38.7	39.7
Hazard Ratio (95% CI)		1.036 (0.827 – 1.297)	0.915 (0.727 – 1.152)
One-sided log-rank p-value[1]		0.76	0.45
Final OS analysis, data cut-off August 26th 2011 (ITT)			
	CPP (n= 625)	**CPB15 (n= 625)**	**CPB15+ (n= 623)**
Median OS (months)	40.6	38.8	43.8
Hazard Ratio (95% CI)		1.07 (0.91,1.25)	0.88 (0.75,1.04)
One-sided log-rank p-value[1]		0.2197	0.0641

Table 2: Overall survival analyses in ICON7

Initial interim OS analysis, data cut-off February 28th 2010 (ITT)		
	CP (n= 764)	**CPB7.5+ (n=764)**
Deaths, n (%)	130 (17)	111 (15)
Median (months)	Not yet reached	
Hazard ratio (95% CI)	0.81 (0.63; 1.04)	
P-value	0.098	
1 Yr OS rate (%)	93	95
Updated interim OS analysis, data cut-off November 30th 2010 (ITT)		
	CP (n= 764)	**CPB7.5+ (n=764)**
Deaths, n (%)	200 (26)	178 (23)
Median (months)	Not yet reached	
Hazard ratio (95% CI)	0.85 (0.69; 1.04)	
P-value	0.1167	
1 Yr OS rate (%)	86	92
Updated interim OS analysis, data cut-off November 30th 2010 (high-risk subgroup)		
	CP (n=234)	**CPB7.5+ (n=231)**
Deaths, n (%)	109 (47)	79 (34)
Median (months)	28.8	36.6
Hazard ratio (95% CI)	0.64 (0.48 – 0.85)	
P-value	p = 0.002	
1 Yr OS rate (%)	86	92

- **Subgroup analyses are reported as February 2010 which suggests that there should be later results available for consistency with the primary PFS results (page 82).**

In GOG-0218 PFS subgroup analyses were an exploratory endpoint and they were analysed on the same dataset as the primary PFS analysis (September 2010). These results are shown on Page 82-83 and Table 13. Although PFS was then updated at a later time point, no secondary or exploratory endpoints (with the exception of OS, which was immature at the time of primary PFS analysis) were re-evaluated.

The analysis of PFS by disease Stage and debulking status (Table 14, Page 84) were provided at the request of the EMA, only for the data from February 2010.

A4. **Please supply p-values for:**

- **Updated PFS analysis (for both groups), page 82.**

These data (ICON-7 and GOG-0128) are obtained from the NEJM 2011 publications; no p-values are reported for this analysis, only HR and 95% CI.

- **Table 14, page 84. Comparison of PFS results by disease stage and debulking status from GOG-0218 for the CPP, CPB15 and CPB15+ groups**

These data are obtained from the Avastin® (bevacizumab) Summary of Product Characteristics; no p-values are reported, only HR and 95% CI

- **All the comparisons between trial groups for each of the 5 time points for the FACT-O TOI results from GOG-0218 (pages 86 – 87).**
- **Table 20, page 93. Comparison of PFS results by disease stage and debulking status from ICON7 for the CP and CPB7.5+ groups**
- **Table 23, page 102. Comparisons of exposure to bevacizumab/ placebo and chemotherapy in the GOG-0218 study for the CPP, CPB15 and CPB15+ groups**
- **Table 30, page 109. Comparisons of the dose and duration of therapy in ICON7 for the CP and CPB7.5+ groups**

P-values are not available for these evaluations.

A5. **For the updated PFS analysis (August 2011), please supply the HR and 95% CI for the CPB15 versus CPP comparison and the median PFS months for the CPP, CPB15 and CPB15+ groups (page 82).**

The results of this updated analysis are from the NEJM 2011 publication, which does not show these median values or the HR for CPB15.

A6. **Please clarify whether the PFS pre-planned subgroup analyses for both Study GOG-0218 (Table 14) and Study ICON7 (Table 18 and Table 20) are adequately powered to detect a statistically significant difference between treatment arms for the relevant subgroups. If so please supply details of the power calculation.**

GOG-0218

No power calculations are available for the subgroup analyses. However, whether or not sufficient power was available, all of the prognostic subgroups (with the exception of mucinous or clear cell

histology (n=109), tumour grade ≤ 2 (n=285) and normal baseline CA-125 (n=105) (Table 13, page 81)) achieved a statistically significant benefit for the CPB15+ arm vs. control (i.e. the 95% confident intervals did not cross the threshold of 1.00). Given that these were significant with a smaller population size than was required to power the ITT analysis, it can be assumed that sufficient power was available.

ICON7

Stratified Analysis for Progression Free Survival

A Cox regression analysis adjusted for stratification factors was performed to test the robustness of the primary analysis. A summary table for the adjusted and unadjusted Cox regression contains the hazard ratios for treatment compared to reference, including the 95% confidence intervals and p-values from the Wald test. This summary table also includes the p-values from the stratified and unstratified log-rank test, testing for a difference in the progression free survival distributions of the treatment and the reference group.

Covariate Factors for the Subgroup Analysis

Exploratory analyses (subgroup analyses and Cox regression) on PFS were performed in order to assess the influence of prognostic factors that were expected to have an impact on the efficacy endpoints. Categorical factors were excluded from the analysis if too few patients belonged to a level of a factor. Stratification factors were included in the unstratified model as covariates.

FIGO stage (I, II, III and IV) and maximum diameter of residual tumour (> 1 cm, ≤ 1 cm and microscopic residual disease, no debulking surgery) were separated and displayed in more detail. The estimated hazard ratio for PFS for treatment compared to reference, resulting from the Cox regression model including only treatment as a factor, were presented for each subgroup level together with the corresponding two-sided 95% confidence interval. Forest plots of the hazard ratio and corresponding 95% confidence intervals were produced for all subgroups.

Cox Regression Analyses for Progression Free Survival

The intention of the following analyses was not to provide scientific evidence with regard to the association of any of these factors with the efficacy endpoint but to study the robustness of the results of the primary analyses. If too few patients belonged to a level of a factor, either pooling of categories or exclusion of the factor could be considered.

Multiple Cox regression analyses were performed in order to assess the robustness of the conclusions drawn from the primary analysis of progression free survival. For the primary analysis, all prognostic factors mentioned above were included in the model and other factors could be added. Age was included as a continuous variable. In case differences were seen between the adjusted and unadjusted model, i.e. the model with treatment as the only factor, further analyses were to be carried out to explain the inconsistencies.

Treatment effect adjusted for each covariate

The univariate Cox analysis was conducted by including only one covariate, with and without treatment, in the regression model. In the model that contained only the covariate, the null hypothesis of the Wald test was that the covariate had no influence on PFS. In the model including both, covariate and treatment, the null hypothesis of the Wald test was that treatment adjusted for

the covariate had no influence on PFS. All covariates which were significant at the 0.15 level in the univariate analysis were included in a multivariate model, then backwards selection at the 5% level was performed to obtain a final model.

A7. **For the ICON7 study please explain why the numbers of patients in Stage III suboptimally debulked plus patients in Stage IV presented in Table 20 do not match the numbers presented in Table 18.**

Table 18 shows results for FIGO stage III suboptimally debulked and FIGO stage IV patients with debulking. Not all Stage III and IV patients in ICON7 were debulked. Table 20 shows the results for all the patients in each Stage.

A8. **In section 1.6 on page 12, it is stated that there are no ongoing or complete studies likely to provide additional evidence in the next 12 months. However, in section 2.6 on page 22 reference is made to "three ongoing studies of carboplatin plus dose-dense or conventional paclitaxel … two of which include concomitant use of bevacizumab". Please clarify which two studies include concomitant use of bevacizumab (i.e. GOG-262, ICON8 or OCTAVIA). Please also clarify the patient populations and doses of bevacizumab examined in these studies and whether or not evidence from these studies is likely to be available in the next 12 months.**

The GOG-0262 and OCTAVIA studies both include concomitant use of bevacizumab. OCTAVIA is a single-arm study of weekly paclitaxel with 3-weekly carboplatin and bevacizumab. It recruited the same range of patients as ICON7 and they were treated for up to 12 months with bevacizumab at 7.5mg/kg. An initial analysis of PFS in OCTAVIA will be reported in October 2012.

GOG-262 is a study of carboplatin and paclitaxel plus bevacizumab 15mg/kg, all given 3-weekly, versus weekly paclitaxel plus 3-weekly carboplatin and bevacizumab. Because both arms of this study contain bevacizumab it cannot provide evidence for the efficacy of bevacizumab. Initial efficacy data are due in June 2013.

A9. **Please clarify the method used to impute missing data for the FACT-O TOI measure when fewer than 50% of items were missing on a subscale for a patient (page 67).**

The imputation of missing data followed the mean value imputation method. (http://nces.ed.gov/statprog/2002/appendixb3.asp)

A10. **On page 68 it is stated that "Following the protocol specifications with modifications, three hypotheses regarding whether FACT-O TOI scores reported by patients during the treatment period over time are independent of treatment received will be tested". Please clarify what modifications were made.**

This statement was taken directly from the statistical analysis plan in the protocol. We have been unable to discover what 'modifications' are referred to.

A11. **Please clarify whether or not the "exploratory" subgroup analyses in the GOG-0218 study detailed on page 72 were planned or post-hoc analyses.**

The GOG-218 protocol states:-

"The final [PFS] analysis will also include exploratory analyses to assess the consistency of the treatment effect on PFS across subgroups of patients determined by presence of clinically measurable of disease (clinically measurable vs non-measurable), site of primary disease (ovarian vs extra-ovarian), stage of disease (III-optimal vs III suboptimal vs IV), histologic cell type (papillary serous vs mucinous vs clear cell vs other cell types), Grade (1 and 2 vs 3) and age (<60 vs >60 years). The exploratory analysis also will include an estimate of the treatment hazard ratios among only those patients deemed eligible for the study."

Therefore the majority of the subgroup analyses shown on Page 72, which substantiate the PFS benefit seen in the primary analysis, were pre-planned. In addition, in GOG-218 performance status was a stratification factor, so this analysis was pre-planned. The only post-hoc subgroup analyses were for race, baseline SLD and baseline CA-125 values.

A12. **Please provide information on the relative risk, risk difference and associated 95% confidence intervals for each adverse event in Tables 24 (page 103), 25 (page 104), 26 (page 105), 28 (page 108), 29 (page 108), 31 (page 109), 32 (page 110), and 33 (page 111). Please also provide the same information for the following statement on page 112: "More deaths from adverse events were observed in the two bevacizumab-containing arms … compared with the control arm" for the GOG-0218 study.**

The data for Adverse Events were not analysed in this fashion, so these results are not available.

A13. **On page 103, in the adverse events section, it is stated that Table 25 (page 104) shows adverse events that "showed a ≥5% difference between arms of the GOG-0218 trial". Why are only adverse events with this difference between groups shown? Furthermore, please clarify why only adverse events reported with a ≥10% difference between groups have been commented on as differing between groups – were these the only statistically significant differences in adverse events reported between the groups?**

The Adverse Events were summarised in the GOG-0218 Clinical Study Report as events which showed a > 5% difference between arms, in order to demonstrate where the major differences lie between safety in the bevacizumab arm and the placebo arm. It is not possible to determine whether the differences between the bevacizumab and placebo arm for each named Adverse Event are statistically significant, because this type of multiple statistical testing on a single dataset requires a Bonferroni correction to reduce the p-value every time a significance test is run. When commenting in the text on the most frequent Adverse Events, we chose 10% (1% for special interest events) as an arbitrary threshold and referred the reader to the table for full information, as there is no value in repeating exactly what is stated in the table. This does not imply the presence, or absence, of other differences in Adverse Events.

A14. **Please provide references for the original sources of the FACT-O TOI, Ovarian Cancer Subscale, and abdominal discomfort score (ADS) quality of life measures used in the GOG-0218 study and for the measures used in the ICON7 study (page 58). Please also provide information or references to sources about their reliability and validity.**

FACT-O TOI

FACT-O TOI was developed by FACIT.org (Functional Assessment of Chronic Illness Therapy). Further details are available on their website (www.facit.org).

FACT-O was adapted from the initial FACT scale, the development and validation of which is described by Cella et al:

Cella, D.F., Tulsky, D.S., Gray, G., et al. (1993). The Functional Assessment of Cancer Therapy (FACT) scale: Development and validation of the general measure. Journal of Clinical Oncology, 11(3), 570-579.

FACT-O is a three-part assessment which includes the Ovarian Cancer Subscale, and is validated in the following reference:

Basen-Enquist, K, Bodurka-Bevers, D., Fitzgerald, M.A., et al(2001). Reliability and validity of the Functional Assessment of Cancer Therapy-Ovarian (FACT-O). Journal of Clinical Oncology, 19(6), 1809-1817.

Abdominal Discomfort Score

Wenzel L, Huang H, Cella D, et al. Validation of FACT/GOG-AD subscale for ovarian cancer-related abdominal discomfort: A Gynecologic Oncology Group study. Gynecol Oncol 2008;110:60-64

EORTC QLQ-C30 & QLQ-OV28

These measures were developed by the European Organization for Research and Treatment of Cancer (http://groups.eortc.be/qol/), and the primary references are:

QLQ-C30: *Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76*

QLQ-OV28: *Greimel E, Bottomley A, Cull A et al. on behalf of the EORTC Quality of Life Group and the Quality of Life Unit. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. Eur J Cancer 39: 1402-1408, 2003.*

EQ-5D

The EuroQOL EQ-5D (http://www.eurogol.org/) primary references are:

The EuroQol Group (1990). EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 16(3):199-208.

Brooks R (1996). EuroQol: the current state of play. Health Policy 37(1):53-72.

A15. **Please clarify what is meant by 'MRC endorsed subgroup analysis' from the ICON7 study (page 6).**

This reflects the subgroup at high risk for progression, as published in the NEJM 2011 by Perren, Swart et al with corresponding author Max Parmar of the MRC Clinical Trials Unit.

Section B: Clarification on cost-effectiveness data

A1. **Please clarify the method, source and probabilities used in the model for the transition between the health states from PFS to death.**

With regards to the model based on the ICON7 study, the probabilities of being in PFS, PD or Death states are taken directly from the observations of patients in the 2 arms of the trial itself. In contrast, the model based on the GOG-0218 study used a mixture of methods to calculate the proportion of patients in each of the 3 health states at any given time.

The following information was omitted from the submission (Section 7.2.2, page 131) in error.

The number of patients in each treatment arm dying from any cause while in PFS was used to derive a constant rate and probability of mortality (Table 3). In the GOG-0218 model, the rate of mortality from the progression-free state was assumed to be at least as great as the underlying sex- and age-related mortality in the general population.

Table 3: Monthly and weekly mortality rates and probabilities from GOG-0218

	BEV + CHEMO	CHEMO
No of PFS Deaths	26	14
PFS Person Weeks	31817.24	28002.82
PFS weekly mortality probability	0.000817	0.000500

Those not transitioning to the death state from PFS were assumed to have progressed disease and transitioned to the PD state. Subsequent transition from PD to death was described in section 7.3.1.2 (p 137).

A2. **Please provide details of the parameter ranges and distributions used for the input parameters in the PSA.**

The following information is provided in Section 7.3.6 (p 142) of the submission.

In order to explore parameter uncertainty around inputs used in the base case analysis, distributions were applied to the following parameters within the model:

- Utility values
- Parameter estimates for the parametric PFS and OS functions (as appropriate)
- Costs and frequency of adverse events
- Weekly supportive care costs in both the PFS and Progressed health states

No distributions were applied for to the cost of medication (bevacizumab, carboplatin or paclitaxel), treatment administration or duration or costs of treatments received following progression (i.e. post-progression treatments in ICON7 and palliative care costs for both models).

Table B1 Summary of variables applied in the economic model

Variable	Value	Measure of variance (distribution)	Reference to section in submission
Patient characteristics		**SD (Log Normal)**	
Age	56.34	N/A	Section 7.5.5
Weight	60.49	13.08	
Height	161.87	N/A	
BSA	1.71	0.1802	
Utilities		**SE (Beta)**	
PFS			
Weeks 0-2	0.6571	0.0133	Section 7.4.3
Weeks 3-5	0.7153	0.0118	
Weeks 6-8	0.7443	0.011	
Weeks 9-11	0.7683	0.01	
Weeks 12-14	0.7643	0.0112	
Weeks 15-20	0.7444	0.0121	
Weeks 21-26	0.7638	0.0131	
Weeks 27-32	0.7718	0.0129	
Weeks 33-38	0.7638	0.0136	
Weeks 29-44	0.7785	0.0155	
Weeks 45-50	0.7533	0.0165	
Weeks 51-53	0.776	0.017	
Weeks 54 +	0.8129	0.0113	
PD	0.7248	-	
Costs		**(Gamma)**	
Expected cost of bevacizumab per visit			
First visit administration and pharmacy costs	£274.57	upper and lower quartiles from NHS Reference costs	Section 7.5.5.5 and 7.5.5.6
Subsequent visit administration and pharmacy costs	£94.27	upper and lower quartiles from NHS Reference costs	
Weekly Supportive Care Costs (£)			
PFS (£)	£10.31	+/- 10%	Section 7.5.6
PD (£)	£44.10	+/- 10%	

When sampling around the parameter estimates for the parametric functions for PFS and OS (or PPS as appropriate, see Table 4) the variance/covariance matrix with Cholesky Decomposition was used. Kaplan-Meier survival estimates of PFS and OS taken directly from the clinical trials were not subject to uncertainty.

Table 4: Parameter estimates (and standard error) for the parametric functions used to model PFS and OS (or PPS).

		PFS		PPS	
GOG-0218	**Parameter**	**Value**	**S.E.**	**Value**	**S.E.**
Chemotherapy	Intercept	2.53771587	0.03812312	3.6499	0.0836
	Scale	0.47388969	0.02178544	1	0
Bev+Chemo	Intercept	2.92295956	0.046566	3.6465	0.0937
	Scale	0.5114776	0.026849	1	0
Combined	Intercept	-	-	3.6484	0.0624
	Scale	-	-	1	0
ICON7		**PFS**		**OS**	
	Intercept	2.717468	0.042734	3.67213536	0.07549945
	Placebo	-0.32093	0.060938	-0.29777142	0.09505761
	Scale	0.389888	0.016296	0.52942336	0.03261643