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ASSESSMENT REPORT FOR AVASTIN

International non-proprietary name/Common name: bevacizumab
Procedure No. EMEA/H/C/582/II/0024

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. Introduction

Avastin (bevacizumab) is a recombinant humanized monoclonal antibody that selectively binds to all isoforms of and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with the complementarity determining regions of a humanized murine antibody that binds to VEGF. Bevacizumab consists of 214 amino acids and has a molecular weight of approximately 149 kD.

Bevacizumab binds to vascular endothelial growth factor (VEGF) and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF reduces the vascularisation of tumours, thereby inhibiting tumour growth. Avastin is currently authorised among other indications for the treatment of metastatic breast cancer in combination with paclitaxel containing chemotherapy.

Paclitaxel and docetaxel share similar chemical structures and anti-tumour activities but differ in haematological toxicity profiles. The present consensus is that both taxanes are active in treating mBC when used as either single agents or in combination therapy and the toxicities associated with each are clinically manageable. The use of bevacizumab with paclitaxel is approved for first-line treatment of mBC. This combination resulted in a statistically significant benefit for patients with a significant improvement over paclitaxel alone in progression-free survival and objective response rate and with an acceptable safety profile, although some doubts with regard to the methodology of the pivotal trial E2100 were raised. As docetaxel is widely used as first-line treatment in mBC, there is a rationale for combining bevacizumab with docetaxel. Furthermore, there is evidence from preclinical studies that bevacizumab together with docetaxel exhibit synergistic antiangiogenic activity, as assessed by endothelial cell proliferation and tubule formation.

2 Clinical aspects

The evaluation of the efficacy of bevacizumab at doses of 7.5 and 15 mg/kg q3w in combination with docetaxel in patients with locally recurrent or mBC is based on the results of one pivotal Phase III, double-blind, placebo-controlled study (BO17708). The submission of the results from study BO17708 fulfils post-approval commitments following the review of the initial application to register bevacizumab as first-line treatment of mBC in combination with paclitaxel based on the E2100 study.

The design of the pivotal phase III study, BO17708, is consistent with established standards, carried out in accordance with the EMEA Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev.3/Corr) and conforming with the principles outlined in the Guideline for Good Clinical Practice ICH Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the subject. The study was approved by the institutional review board or ethics committee of each participating centre. The full package of data provided in this application is given in Table 1 below:

Table 1. Data submitted.

Protocol No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Admin.	Number of Patients	Diagnosis of Patients Main Inclusion Criteria	Duration of Treatment	Study Status; Type of Report
BO17708	Comparison of the efficacy of docetaxel plus bevacizumab to docetaxel plus placebo. Primary: Progression free survival Secondary: Best overall response, duration of response, overall survival, time to treatment failure, quality of life.	Phase III, randomized, double-blind, multicenter, placebo controlled	Bv7.5+Doc q3w[a] Bv15+Doc q3w[b] Pl+Doc q3w[c]	248 247 241	Locally recurrent or metastatic breast cancer. HER2-negative. Not previously treated with chemotherapy.	Bv: Unlimited Doc: 9 cycles	Follow-up for overall survival. Full CSR.
Publication	**Ramaswamy B,** Elias AD, Kelbick NT et al. Phase II trial of bevacizumab in combination with weekly docetaxel in metastatic breast cancer patients. Clin Cancer Res. 2006;12(10):3124-3129						
Publication	**Wedam SB,** Low JA, Yang SX et al. Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer. J Clin Oncol. 2006;24(5):769-777.						

2. 1. Pharmacokinetics

No new studies have been performed in support of this application. The clinical pharmacology of bevacizumab has been extensively investigated in previous studies. However, pharmacokinetic parameters have not been evaluated with concomitant docetaxel.

2. 2. Pharmacodynamics

The mechanism of action of bevacizumab is well known. No new data on pharmacodynamics are presented.

2. 3. Clinical efficacy

Dose-response studies
No new dose-response studies are presented for the present study.

Two doses of bevacizumab were selected in the pivotal study BO17708; each dose in combination with docetaxel was tested against placebo with docetaxel for efficacy. The higher dose of bevacizumab was chosen to be 15 mg/kg q3w, the same dose as that used in study E2100, the pivotal study which tested paclitaxel alone vs. paclitaxel plus bevacizumab (10 mg/kg q2w, i.e., 5 mg/kg weekly equivalent), and which was subsequently approved for the treatment of mBC.

The applicant considered it prudent to investigate whether a lower dose would also be effective in mBC; 7.5 mg/kg q3w (i.e., 2.5 mg/kg weekly equivalent) was chosen as this dose had already proven to be efficacious in other indications (mCRC and advanced NSCLC).

No consistent dose-response relationship has been found in the range 2.5 mg/kg/week – 10 mg/kg/week. It is reasonable to test also the lower dose, as is done in the pivotal study. Although two doses of bevacizumab were tested in the study, no formal statistical comparisons of efficacy between the two doses were planned; however, an exploratory analysis was conducted. The dosing schedule for both doses used in study BO17708 (q3w) was chosen to be in alignment with the frequency of the chemotherapy regimen (docetaxel).

The dose of docetaxel used in this study (100 mg/m^2) is that currently approved in the EU for use as monotherapy in the treatment of mBC. Because there are no other extensive studies exploring bevacizumab in combination with docetaxel, the full safety profile, including the potential for overlapping toxicities, has not been established previously. The same starting dose of docetaxel in all arms was therefore used to help maintain homogeneity between groups and facilitate the interpretation of the study. It is also noted that docetaxel as monotherapy is not indicated for first line treatment of breast cancer (EPAR Taxotere).

Main clinical study

The pivotal study BO17708 is a randomised, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of bevacizumab in combination with docetaxel in comparison with docetaxel plus placebo as first line treatment for patients with HER2-negative metastatic and locally recurrent breast cancer. It is a multicenter study sponsored and conducted by F. Hoffmann-La Roche Ltd in 106 centers in 24 countries (Western Europe/Australia/Canada; Eastern Europe; East Asia; Central and South America). The study was randomized and double-blind. Patients and investigators were blinded to the nature of treatment but not to the dose level each patient received. The same vial sizes and volumes of infusate were used for bevacizumab and placebo.

Overall, study BO17708 enrolled a typical mBC population, suitable for first-line therapy with full-dose docetaxel. Pre- and post-menopausal female patients who were at least 18 years of age with histologically or cytologically confirmed HER2-negative, locally recurrent or metastatic adenocarcinoma of the breast were enrolled. Measurable or non-measurable disease was allowed. Patients were candidates for chemotherapy with an ECOG performance status (PS) of 0 or 1. Three patients were HER2-positive, and although being protocol violators, were included in the primary analysis of the ITT population.

Prior non-taxane adjuvant / neo-adjuvant chemotherapy was allowed as long as the last dose of chemotherapy was not within six months of randomization. Patients receiving taxane-containing adjuvant chemotherapy were eligible only if they received their last chemotherapy ≥ 12 months prior to randomization. If chemotherapy was anthracycline-based, the maximum cumulative dose of prior anthracycline therapy could not exceed 360 mg/m^2 for doxorubicin and 720 mg/m^2 for epirubicin.

Patients were excluded if they had other primary tumours within the last five years, had evidence of spinal cord compression or brain metastases, had undergone a major surgical procedure within 28 days of randomization, had pre-existing peripheral neuropathy (NCI-CTC Grade > 2), a history or evidence of central nervous system (CNS) disease, cerebrovascular accident/stroke (≤ 6 months prior to randomization), bleeding diathesis, or clinically significant cardiovascular disease, including myocardial infarction within 6 months of randomization, unstable angina, congestive heart failure (NYHA grade II), or uncontrolled hypertension.

A total of 736 patients were enrolled into study BO17708. The first patient was randomized on March 20, 2006 and the last on April 12, 2007. At the time of the clinical cut-off date (October 31, 2007), 185/241 patients (77%) in the Pl + Doc arm, 192/248 (77%) in the Bv 7.5 + Doc arm, and 203/247 (82%) in the Bv 15 + Doc arm were alive (in treatment or in follow-up).

The demographic and baseline characteristics of patients were comparable across the treatment arms. All patients were female (as per the inclusion criteria), the majority were white (~84% in each arm), and the mean age was ~53 years in all three arms. Most patients (73%) were aged between 40 and 64 years of age; 16% - 19% were older than 65 years.

The three treatment arms were well balanced with regard to breast cancer history and previous therapies for breast cancer:

- 96% - 99% of patients had a history of metastatic disease; 1% – 4% of patients had a history of local disease only.
- 81% - 86% had measurable disease at baseline.
- 47% - 48% had well differentiated or moderately differentiated primary tumour at baseline.
- 99% had undergone previous surgery for breast cancer.

- 53% - 55% of patients were previously treated with anthracyclines; 37% - 39% with aromatase inhibitors; 15% - 17% with taxanes.

The treatment arms were reasonably well balanced with respect to the incidence of target and non-target lesions at baseline, the most frequent of which were in the bone (55% - 60%), liver (40% - 50%), and lung (38% - 42%); lymph node metastases were reported in 45% - 53% of patients. Target lesions were in line with this observation. The mean number of lesions and number of sites per patient were also balanced across the three treatment arms.

The primary efficacy endpoint was the duration of PFS defined as the time from randomization to first documented disease progression or death from any cause, whichever occurred first.
Secondary endpoints were:

- Best overall response (OR) defined as either a confirmed complete response (CR) or a confirmed partial response (PR) analyzed in patients with measurable disease at baseline.
- Duration of response (DR) defined as the time interval between when a response (CR or PR) was first documented and disease progression or death occurred.
- Time to treatment failure (TTF) defined as the time between randomization and the date of either disease progression, death or withdrawal of treatment due to adverse events, withdrawn informed consent, insufficient therapeutic response, refusal of treatment / failure to co-operate, or failure to return, whichever occurred first.
- Overall survival (OS) defined as the time between randomization and death due to any cause; the study was not powered for OS but an initial analysis of OS was performed at the time of the final analysis for PFS.
- Change in patients' quality of life scores measured with the FACT-G and FACT-B questionnaires.

Tumour assessments (by the investigators based on RECIST criteria) using CT / MRI / bone scans and X-rays were performed at baseline and every nine weeks until week 36 and thereafter every 12 weeks until disease progression, always within seven days of the scheduled visits. The assessment schedule was identical across the treatment arms. Based on the robust nature of the study design, including blinding, independent radiological review of disease assessment was not mandated. This is in agreement with the EMEA Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev.3/Corr) regarding absence of independent review in properly randomized, blinded trials where investigator evaluation may be sufficiently reliable as a basis for treatment comparisons. However, as trialists may have guessed by the side effects of the treatment which treatment group a given patient was in, bias with regard to tumour assessment cannot be completely ruled out. Clinical examinations were performed before each cycle. Quality of life was assessed on the basis of a change from screening in the scores of the FACT questionnaires at cycles 3, 5, and 11.

The primary population for efficacy analysis was the intent-to-treat (ITT) population which included all patients randomized into the study. Data were analyzed using standard statistical methods including log-rank tests for the comparison of survival distributions, Cox regression models to determine hazard ratios, and Kaplan-Meier curves with median survival estimates and confidence limits.

The primary analysis of PFS was based on an unstratified analysis and included all progression events. A closed test procedure was employed to adjust for the multiplicity of testing (comparing the two bevacizumab-containing arms against the placebo arm). Sensitivity analyses (PFS on treatment, PFS before the start of non-study anti-neoplastic treatment) were performed to test the robustness of the results. The analysis censored for non-study anti-neoplastic treatment (the primary analysis in study E2100) allows for an assessment of the treatment benefit that is not confounded by the effect of additional cancer treatments started prior to disease progression. In addition, 'worst case' analyses (to investigate the effect of incomplete follow-up information; to investigate the effect of missing tumour assessments) were performed to assess the consistency of the results and the impact of different censoring rules on the analysis of PFS. All key analyses of PFS were performed in an unstratified and a stratified manner, with the stratification factors used for randomization. A stratified analysis gives a more accurate estimate of the treatment effect if the prognostic factors are truly prognostic, as variability between patients is reduced in this type of analysis.

	Table 2 Overview of Efficacy for Study BO17708: Original and Updated Analysis (ITT Population) – as per September 2008					
	Original analysis			Updated analysis		
Parameter	**Pl + Doc[a] N = 241**	**Bv 7.5 + Doc[b] N = 248**	**Bv 15 + Doc[c] N = 247**	**Pl + Doc[a] N = 241**	**Bv 7.5 + Doc[b] N = 248**	**Bv 15 + Doc[c] N = 247**
PFS (unstratified)						
Patients with events	162	149	142	214	218	208
Median PFS	8.0 months	8.7 months	8.8 months	8.2 months	9.0 months	10.1 months
Log-rank test p-value (unadjusted)**		0.0318	0.0036			
Hazard ratio* (95% CI)	-	0.79 (0.63; 0.98)	0.72 (0.57; 0.90)	-	0.85 (0.70; 1.02)	0.75 (0.62; 0.91)
PFS (stratified) censored for subsequent antineoplastic therapy						
Patients with events	154	137	135	195	191	191
Median PFS	8.0 months	8.7 months	8.8 months	8.0 months	9.0 months	10.0 months
Log-rank test p-value**		0.0035	< 0.0001			
Hazard ratio* (95% CI)	-	0.69 (0.54; 0.89)	0.61 (0.48; 0.78)	-	0.77 (0.62; 0.95)	0.67 (0.54; 0.83)
Overall response rate[d], n (%)	92 (44.4%)	111 (55.2%)	130 (63.1%)	95 (45.9%)	111 (55.2%)	132 (64.1%)
Chi-squared Test p-alue**		0.0295	0.0001			
Complete response	1.0%	3.0%	1.0%	1.0%	4.5%	2.9%
Partial response	43.5%	52.2%	62.1%	44.9%	50.7%	61.2%
Stable disease	38.6%	35.3%	24.8%	37.2%	34.3%	24.3%
Progressive disease	11.6%	4.5%	4.4%	11.1%	3.5%	3.4%
Duration of response[d]						
Patients with events	53	58	68	65	72	81
Median duration of response	6.4 months	7.2 months	7.0 months	6.9 months	8.5 months	8.5 months
Hazard ratio* (95% CI)	-	0.74 (0.51; 1.08)	0.80 (0.56; 1.14)	-	0.88 (0.63; 1.24)	0.80 (0.58; 1.11)
Time to treatment failure						
Patients with events	188	185	186	226	233	224
Median time to treatment failure	6.1 months	7.0 months	7.7 months	6.3 months	7.7 months	7.9 months
Log-rank test p-value**		0.1105	0.0241			
Hazard ratio* (95% CI)	-	0.85 (0.69; 1.04)	0.79 (0.65; 0.97)	-	0.86 (0.71; 1.03)	0.79 (0.66; 0.95)
Overall survival (unstratified)						
Patients with events	50	49	37	89	97	92
Median time to death	n.d.	n.d.	n.d.	n.d.	27.6	27.6
Log-rank test p-value**		0.6962	0.0765			
Hazard ratio* (95% CI)	-	0.92 (0.62; 1.37)	0.68 (0.45; 1.04)	-	1.03 (0.77; 1.37)	0.94 (0.71; 1.26)

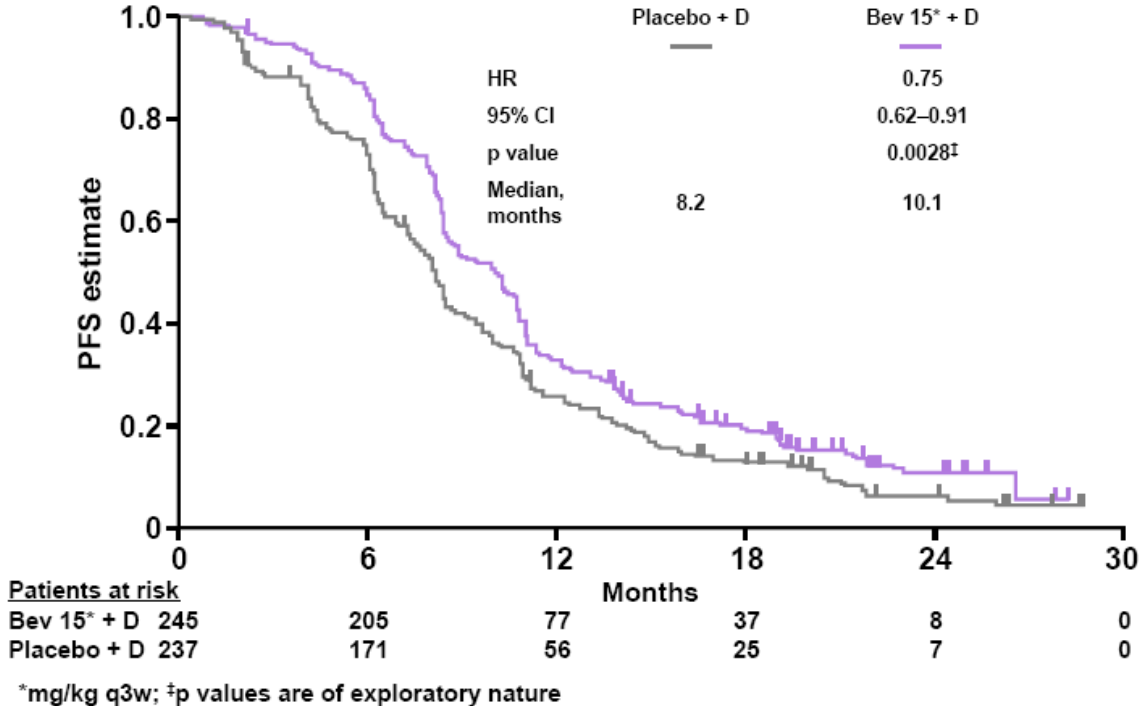
[a] Bevacizumab placebo + Docetaxel 100 mg/m^2 q3w; [b] Bevacizumab 7.5 mg/kg + Docetaxel 100 mg/m^2 q3w; [c] Bevacizumab 15 mg/kg + Docetaxel 100 mg/m^2 q3w; [d] Analysis based on ITT population with measurable disease at baseline; * Hazard ratio versus Pl + Doc arm; ** p-value for the comparison with the Pl + Doc arm; n.d. not determined

Primary Endpoint - Progression-Free Survival

Updated results as of 15 September 2008 have been presented. They show a somewhat larger and more sustained effect on PFS of the higher dose of bevacizumab, with a median prolongation of PFS of nearly 2 months, which is due to the fact that the two curves no longer accidentally come very close to each other at the median survival. It is reassuring that the difference seems to be sustained between 12 and 24 months, but the actual difference in PFS is still a maximum of about two months.

The applicant has elected to present only data for the higher dose of bevacizumab, since this is the dose being carried forward as the recommended dose. This is reasonable since the higher dose seems to consistently give better results. The PFS curves for placebo vs. the higher dose of bevacizumab are seen below, demonstrating the fact stated above that the maximum difference is still about two months.

Figure 1 Kaplan Meier Plot of Progression-Free Survival for Pl + Doc vs. Bv 15 + Doc (ITT Population – Updated Unstratified Analysis)



*mg/kg q3w; ‡p values are of exploratory nature

Secondary Endpoints

Best Overall Response and Duration of Response

In patients with measurable disease, both Bv + Doc arms showed a higher OR (CR + PR) rate compared with Pl + Doc (55,2% in Bv 7.5 + Doc and 64,1% in Bv 15 + Doc vs 45,9% in Pl + Doc). The absolute difference in OR rates between each of the Bv + Doc arms compared with Pl + Doc (9.1% and 18.2%, respectively) was statistically significant. However, virtually all responses were only partial. This was partly correlated with a higher percentage of progressive disease in the control arm, but also with a higher percentage of stable disease. The overall benefit of the higher partial response rate in this scenario must be regarded as very modest.

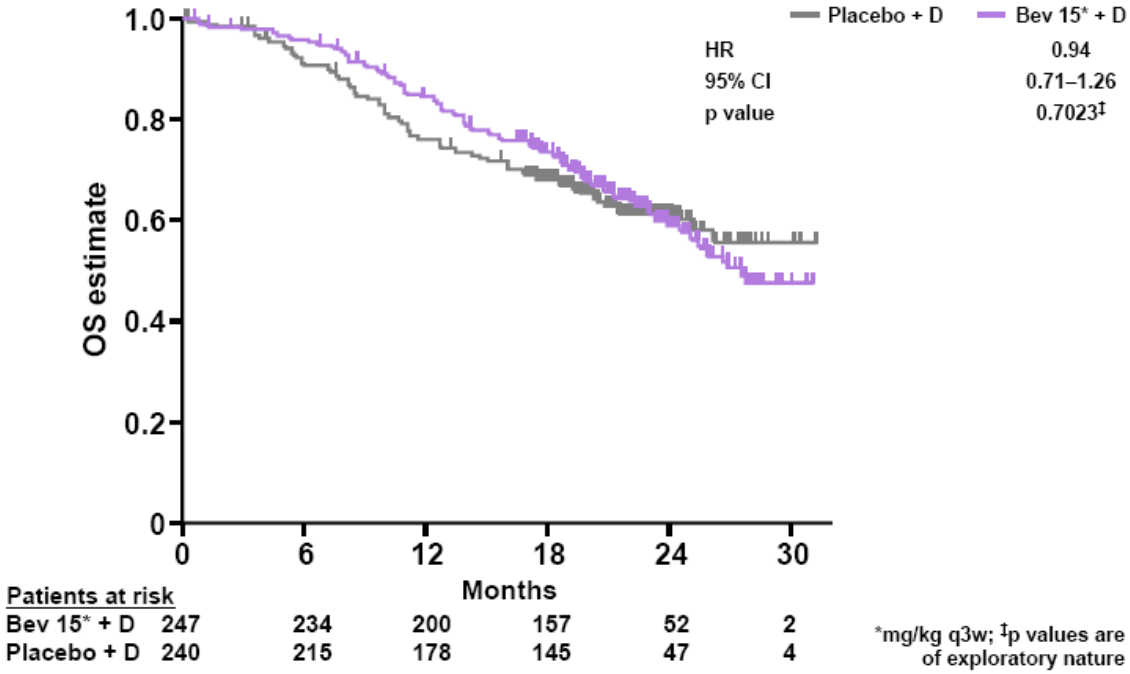
The median duration of response was slightly longer in the Bv + Doc arms compared with the Pl + Doc arm (8.5 months in Bv 7.5 + Doc and 8.5 months in Bv 15 + Doc vs 6.9 months in Pl + Doc). The difference in duration of response is even smaller than the difference in PFS.

Overall Survival

The initial data package contained immature overall survival data, and more overall survival data was asked for continuously in the 1st and 2nd assessment. The trial was not powered for OS, nevertheless, a more mature analysis of OS will be performed when all patients enrolled in the study have been followed for a minimum of 24 months.

Below is shown the updated survival curves as of September 2008, demonstrating no significant difference between the placebo arm and the higher dose bevacizumab arm. At about 18 months the curves converge and they cross over at 24 months. It is clear, as the applicant states, that there is a lot of censoring after 18 months, and it is true, as the applicant states, that at this point the curves become fairly unreliable. However, it is a cause for concern that the trend goes in that direction, and more certain data on overall survival in the second year after treatment will be important before deciding if this treatment is safe.

Figure 2 Kaplan Meier Plot of Overall Survival for Pl + Doc vs. Bv 15 + Doc (ITT Population – Updated Unstratified Analysis)



The applicant argues strongly in the response to the previous questions that the survival curves should only be analysed up to about 15 months. A summary of the results up to that point is shown in the table below.

Table 3 Summary of Survival up to 15 Months of Follow−up

	Pl+doc (N=241)	Bv7.5+doc (N=248)	Bv15+doc (N=247)
Patients with event	66 (27.4 %)	60 (24.2 %)	54 (21.9 %)
Patients without events*	175 (72.6 %)	188 (75.8 %)	193 (78.1 %)
Time to event (months)			
p-Value (Log-Rank Test)		0.3716	0.1188
Hazard Ratio		0.85	0.75
95% CI		[0.60;1.21]	[0.52;1.08]

Time to CSDIED [months] (TTMDIED) - Censoring: Overall Survival (CSDIED)
* censored
# Kaplan-Meier estimate
including censored observations

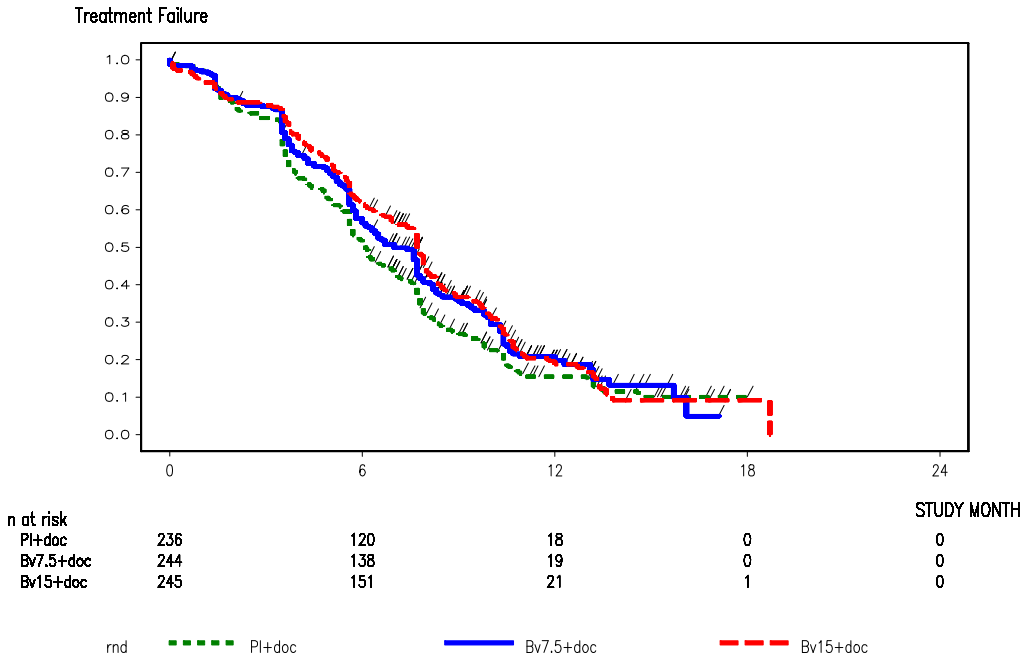
The applicant goes on to present overall survival analyses on subgroups of patients, depending on whether or not they got post-study bevacizumab. These analyses all point in a better direction than the overall analysis presented above, but these analyses must be regarded with scepticism as they represent non-planned subgroup analyses.

Time to Treatment Failure

In the previous submissions the data showed that more patients in the Pl + Doc arm (78%) experienced treatment failure than in either of the Bv + Doc arms (75%). Updated analysis shows that time to treatment failure in the Bv 15 + Doc arm was statistically significantly longer than in the Pl + Doc arm. In the Bv 7.5 + Doc arm the difference was not statistically significant (0.86).

Median time to treatment failure was 6.3 months in the Pl + Doc arm and 7.7 and 7.9 months in the Bv 7.5 + Doc and Bv 15 + Doc arms, respectively. The modest difference in TTF is similar to the modest difference in PFS. In the updated analysis the difference with regard to TTF is still modest, although the difference in PFS has become somewhat larger.

Figure 3 Kaplan Meier Curve of Time to Treatment Failure: Study BO17708 (ITT Analysis Population)



Quality of Life

The addition of bevacizumab to docetaxel did not lead to an overall deterioration in the mean quality of life scores (total FACT-B and FACT-G scores) compared to the addition of placebo to docetaxel. Where improvements from screening in mean quality of life scores were seen in the Bv + Doc arms, this was mainly driven by an improvement in emotional well-being. For the FACT-B score, which is specific for breast cancer, improvements were generally seen in both Bv + Doc arms compared with the Pl + Doc arm at all time points after screening, and were particularly noticeable at cycle 11. The additional toxicity of combining bevacizumab with docetaxel did not appear to impact negatively on patients' quality of life. However, the differences reported in the QoL scores are small, and results are conflicting. It is stated by the applicant that the addition of bevacizumab does not lead to an overall deterioration in QoL scores, which is in accordance with the findings in many other studies of this kind. QoL scores are notoriously insensitive, so the information value from this analysis is limited. Further analyses of the QoL data did not reveal any difference between the treatment groups.

Efficacy in Subgroups

The results of each of the subgroup analyses for PFS were generally consistent with those seen for all patients, indicating that the results of this trial are robust and not driven by a particular subgroup. These analyses do not give cause for suspicion that there were any subgroups with a qualitatively different effect of the addition of bevacizumab to docetaxel. However, because of the very modest overall effect on PFS the confidence intervals for most subgroups cross the equivalence line, especially for the lower dose of bevacizumab.

Analysis of Clinical Information Relevant to the Dosing Recommendations

Doses of bevacizumab of 7.5 mg/kg and 15 mg/kg given every three weeks in combination with 100 mg/m2 docetaxel as first-line treatment for locally recurrent or metastatic breast cancer in study BO17708, both doses in the original analyses showed a statistically significant reduction in the risk of progression or death by 21% and 28%, respectively, compared with the control arm of placebo plus docetaxel. Although the risk reduction seen with the higher dose of bevacizumab was numerically

greater than that seen with the lower dose, an exploratory comparison did not reveal a statistically significant difference in PFS between the two bevacizumab doses.
However, while both doses of bevacizumab in combination with docetaxel were efficacious in this trial and showed increases in PFS which were statistically significant compared to the control, the higher dose of bevacizumab (15 mg/kg q3w - 5mg/kg/wk weekly equivalent) consistently showed a numerical advantage across a range of secondary efficacy endpoints compared to the lower dose of bevacizumab (7.5 mg/kg q3w - 2.5 mg/kg/wk equivalent). In addition in the updated analysis, the lower dose; 7.5 mg/kg was not superior to control for PFS, OR rate and 1-year survival. It must be stressed that the BO17708 study was not dimensioned to show any difference between the two doses. The evidence presented points in the direction of a larger effect of the 15 mg/kg dose, but no significant difference between the two dose levels has been documented.

Clinical studies in special populations
There are no clinical studies in special populations presented.

Efficacy Results across Studies
In the previous submissions key efficacy results from the current study of bevacizumab in combination with docetaxel (BO17708) and the previously submitted study with bevacizumab in combination with paclitaxel (E2100) were presented. Both studies showed a statistically significant improvement in the primary endpoint of PFS. The main statistical analyses of PFS were slightly different in the two studies.

Table 4 Comparison of PFS Results of Studies E2100 and BO17708

	Study E2100		**Study BO17708**		
Progression Free Survival#	**Pac (n=354)**	**Bv 10 + Pac (n=368)**	**Pl + Doc (n=241)**	**Bv 7.5 + Doc (n=248)**	**Bv 15 + Doc (n=247)**
Unstratified HR (95% CI), not censored for NPT	0.63 (0.52; 0.77)			0.79 (0.63; 0.98)* *0.85 (0.7; 1.02)***	0.72 (0.57; 0.90)* *0.75 (0.62; 0.91)***
Median (months)	6.1	11.2	8.0* *8.2***	8.7* *9.0***	8.8* *10.1***
Stratified HR (95% CI), censored for NPT	0.48 (0.39; 0.61)			0.69 (0.54; 0.89)* *0.77 (0.62; 0.95)***	0.61 (0.48; 0.78)* *0.67 (0.54; 0.83)***
Median (months)	5.8	11.3	8.0* *8.0***	8.7* *9.0***	8.8* *10.0***

* Study BO17708 original analysis**. ** Study BO17708 updated analysis**. # IRF results for E2100 (primary analyses: stratified); investigator-assessed results for BO17708 (primary analysis: unstratified). Bv = Bevacizumab; CI = Confidence interval; Doc = Docetaxel; HR = Hazard ratio; IRF = Independent review facility; NPT = Non protocol antineoplastic therapy; Pac = Paclitaxel; Pl = Placebo

In study BO17708, an unstratified analysis was performed and included all progression and death events that occurred up to the clinical cut-off date. In study E2100, a stratified analysis was performed and included only progression events that occurred prior to start of non-protocol therapy and deaths only if they occurred up to 84 days after last dose of study treatment. When an analysis similar to the primary analysis as used in study E2100 was performed on data from study BO17708, the risk of progression or death was further reduced to 31% (HR 0.69) and 39% (HR 0.61) in the Bv 7.5 +Doc and Bv 15 + Doc arms, respectively in the original analysis and 23% (HR 0.77) and 33% (HR 0.67) in the updated analysis.

<u>Supportive studies</u>
Efficacy data from two small phase II studies of bevacizumab in combination with docetaxel reported as full publications are presented:

- The Phase II trial (sponsored by the Cancer and Treatment Evaluation Program of the National Cancer Institute) of bevacizumab (10 mg/kg q2w) and docetaxel (35 mg/m2 qw) in 27 patients with mBC showed 52% of patients responding (all PR) for a median time of 6 months with median PFS of 7.5 months [Ramaswamy et al]

- The pilot study of bevacizumab (15 mg/kg q3w) with doxorubicin (50 mg/m2 q3w) and docetaxel (75 mg/m2 q3w) in 21 patients with inflammatory and locally advanced breast cancer showed 67% of patients responding (all PR) [Wedam et al]

These studies are uncontrolled and very small, and they do not add any significant information with regard to efficacy.

1. 2. 5. Clinical safety

The evaluation of safety information for bevacizumab in combination with docetaxel as first-line treatment for patients with locally recurrent or metastatic breast cancer is derived from the randomized, double-blind, placebo controlled, Phase III study, BO17708. Safety was assessed by recording all adverse events (with intensity graded according to NCI-CTCAE version 3.0), including adverse events of special interest (attributed to bevacizumab or docetaxel treatment), serious adverse events, vital signs, electrocardiograms (ECGs), and safety laboratory tests.

In addition, safety information from two publications of Phase II studies is included, one of bevacizumab in combination with docetaxel in metastatic breast cancer patients, another of bevacizumab in combination with doxorubicin and docetaxel in patients with inflammatory and locally advanced breast cancer.

Patient exposure
In study BO17708, 497 patients with mBC have been exposed to bevacizumab either at 7.5 or 15 mg/kg q3w in combination with docetaxel. From the two full publications, an additional 27 patients with mBC have received bevacizumab 10 mg/kg q2w in combination with docetaxel; and 21 patients with inflammatory and locally advanced breast cancer have received bevacizumab 15 mg/kg q3w in combination with doxorubicin and docetaxel. Thus, the data are adequate to assess the safety of the combination of bevacizumab and docetaxel. Follow-up has been sufficiently long in the pivotal study to allow a reasonable assessment of safety of this combination in this indication.

In study BO17708, exposure to bevacizumab/placebo and docetaxel based on dose intensity (actual dose received divided by planned dose) was high and similar across the treatment arms (96%-98%).

The median duration of bevacizumab/placebo treatment was greater in the Bv 7.5 + Doc (218 days) and Bv 15 + Doc (232 days) arms than in the Pl + Doc arm (203 days). The median duration of docetaxel treatment was also longer in the Bv 7.5 + Doc (154 days) and Bv 15 + Doc (167 days) arms than in the Pl + Doc arm (148 days).

In the publication by Ramaswamy et al, 48% of patients completed the planned six cycles (q2w). In the publication by Wedam et al, 76% of patients completed the planned seven cycles of therapy (q3w).

The number of patients and data collected for safety evaluation are summarized in Table 3. The two small phase II trials contribute very little information. In effect, the BO17708 study is the only study contributing data on the safety of the combination of bevacizumab and docetaxel.

Adverse Event Experience
An overview of the adverse event experience reported in study BO17708 is shown in the table below. The tolerability profile of the combination of bevacizumab with docetaxel was not markedly different from that of placebo and docetaxel. An increase in overall Grade 3-5 toxicities was seen in the Bv + Doc arms, as expected from the addition of a second drug agent; however, this increase did not translate into a greater number of discontinuations from study treatment. The number of deaths due to progressive disease was lower in the Bv + Doc arms, especially in the Bv 15 + Doc arm (14% vs. 21% in the Pl + Doc arm). The overall incidence of adverse events of special interest (all grades) was higher in the Bv +Doc arms, mainly driven by increases in bleeding (mainly epistaxis, all grades) and hypertension (all grades) in these arms. Despite the numerically higher incidence of all grade epistaxis, hypertension, febrile neutropenia, and proteinuria in the Bv 15 + Doc arm compared with the Bv 7.5 + Doc arm, there was no clinically meaningful difference in the safety profile between the two bevacizumab-containing arms.

Table 5 Overview of Adverse Event Experience, Study BO17708 (Safety Population)

Parameter	Pl + Doc[a] N=233	Bv 7.5 + Doc[b] N=250	Bv 15 + Doc[c] N=247
Patients with at least one:			
Adverse event	232 (99.6%)	250 (100.0%)	246 (99.6%)
NCI-CTC Grade 3, 4, 5 adverse event	156 (67.0%)	187 (74.8%)	183 (74.1%)
Serious adverse event	76 (32.6%)	92 (36.8%)	104 (42.1%)
AE leading to discontinuation (any study drug)	62 (26.6%)	58 (23.2%)	69 (27.9%)
All deaths (including progressive disease)	49 (21.0%)	50 (20.0%)	35 (14.2%)
Deaths due to adverse events[d]	6 (2.6%)	9 (3.6%)	5 (2.0%)
Patients with at least one:			
AE of special interest	140 (60.1%)	188 (75.2%)	193 (78.1%)
NCI-CTC Grade 3, 4, 5 AE of special interest	73 (31.3%)	88 (35.2%)	90 (36.4%)
Serious adverse event of special interest	38 (16.3%)	47 (18.8%)	57 (23.1%)
Adverse event of special interest (all grades)			
Bleeding (all events)[e]	66 (28.3%)	131 (52.4%)	135 (54.7%)
Mucocutaneous bleeding[e]	51 (21.9%)	118 (47.2%)	123 (49.8%)
Pulmonary hemorrhage[e]	2 (0.9%)	3 (1.2%)	5 (2.0%)
Neutropenia	45 (19.3%)	54 (21.6%)	53 (21.5%)
Febrile neutropenia	28 (12.0%)	39 (15.6%)	45 (18.2%)
Hypertension	21 (9.0%)	34 (13.6%)	44 (17.8%)
Venous thromboembolic events	18 (7.7%)	15 (6.0%)	18 (7.3%)
Wound healing complication	3 (1.3%)	8 (3.2%)	12 (4.9%)
Proteinuria	4 (1.7%)	3 (1.2%)	8 (3.2%)
Abscess and fistula	1 (0.4%)	6 (2.4%)	6 (2.4%)
Congestive heart failure	1 (0.4%)	3 (1.2%)	2 (0.8%)
Gastrointestinal perforation	2 (0.9%)	1 (0.4%)	2 (0.8%)[f]
Arterial thromboembolic events	2 (0.9%)	0	1 (0.4%)
RPLS	0	0	0

[a] Bevacizumab placebo + Docetaxel 100 mg/m^2 q3w. [b] Bevacizumab 7.5 mg/kg + Docetaxel 100 mg/m^2 q3w [c] Bevacizumab 15 mg/kg + Docetaxel 100 mg/m^2 q3w. [d] Also includes patients who died more than 21 days after last drug administration. [e] Since patients could have more than one type of bleeding event, the sum of the number of events is larger than the number of patients with bleeding events. [f] Includes one additional patient with a perforated duodenal ulcer not on the database.

In study BO17708, virtually all patients experienced at least one adverse event of any grade between the time of first drug administration and 21 days after the last drug administration; (232 [99.6%] in the Pl + Doc arm, 250 [100%] in the Bv 7.5 + Doc arm and 246 [99.6%] in the Bv 15 + Doc arm).

The conclusion of the analyses of adverse events of all grades was:

- Bevacizumab did not have a major impact on the safety profile of docetaxel
- The safety profile of the combination docetaxel plus bevacizumab was as predicted based on the known toxicities of the two agents administered separately
- Adding bevacizumab to docetaxel as first-line therapy resulted in no unexpected toxicities
- Adding bevacizumab to docetaxel did not increase the rate of withdrawals from treatment due to toxicity
- Deaths were mainly due to progressive disease
- Treatment-related deaths were uncommon in all three treatment arms

Grade 3-5 Adverse Events

More patients in the Bv + Doc arms (74% and 75%) than in the Pl + Doc arm (67%) reported Grade 3-5 adverse evens (table 2 just above + table 3 below), the most common of which were established docetaxel toxicities. The most frequently reported Grade 3-5 adverse events that occurred with a higher incidence in either of the Bv + Doc arms compared with the Pl + Doc arm were neutropenia and febrile neutropenia (table 3). Other events that occurred more frequently (≥ 2%) in either of the Bv + Doc arms compared with the Pl + Doc arm were fatigue, mucosal inflammation, palmar-plantar erythrodysesthesia syndrome, diarrhoea, stomatitis, peripheral sensory neuropathy, skin exfoliation and myalgia (table 3).

Table 6 Summary of Grade 3-5 Adverse Events with an Incidence of at least 2% in any Study Arm, Study BO17708 (Safety Population)

Body System/ Adverse Event	Pl+doc N = 233 No. (%)	Bv7.5+doc N = 250 No. (%)	Bv15+doc N = 247 No. (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
NEUTROPENIA	40 (17.2)	48 (19.2)	49 (19.8)
FEBRILE NEUTROPENIA	28 (12.0)	38 (15.2)	41 (16.6)
LEUKOPENIA	11 (4.7)	16 (6.4)	13 (5.3)
ANAEMIA	6 (2.6)	1 (0.4)	3 (1.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
ASTHENIA	17 (7.3)	19 (7.6)	16 (6.5)
FATIGUE	12 (5.2)	21 (8.4)	16 (6.5)
MUCOSAL INFLAMMATION	1 (0.4)	10 (4.0)	12 (4.9)
OEDEMA PERIPHERAL	5 (2.1)	3 (1.2)	1 (0.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	2 (0.9)	13 (5.2)	15 (6.1)
NAIL DISORDER	8 (3.4)	10 (4.0)	11 (4.5)
ALOPECIA	9 (3.9)	9 (3.6)	9 (3.6)
SKIN REACTION	4 (1.7)	7 (2.8)	5 (2.0)
NAIL TOXICITY	2 (0.9)	1 (0.4)	6 (2.4)
SKIN EXFOLIATION	-	6 (2.4)	3 (1.2)
GASTROINTESTINAL DISORDERS			
DIARRHOEA	8 (3.4)	17 (6.8)	17 (6.9)
STOMATITIS	1 (0.4)	7 (2.8)	8 (3.2)
ABDOMINAL PAIN	4 (1.7)	2 (0.8)	6 (2.4)
VOMITING	3 (1.3)	3 (1.2)	6 (2.4)
INFECTIONS AND INFESTATIONS			
INFECTION	7 (3.0)	2 (0.8)	1 (0.4)
NERVOUS SYSTEM DISORDERS			
PERIPHERAL SENSORY NEUROPATHY	4 (1.7)	8 (3.2)	11 (4.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
MYALGIA	2 (0.9)	3 (1.2)	9 (3.6)
BONE PAIN	4 (1.7)	3 (1.2)	6 (2.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
DYSPNOEA	4 (1.7)	6 (2.4)	7 (2.8)
METABOLISM AND NUTRITION DISORDERS			
ANOREXIA	2 (0.9)	2 (0.8)	5 (2.0)
VASCULAR DISORDERS			
HYPERTENSION	3 (1.3)	-	7 (2.8)

Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.

Deaths not due to Progressive Disease

The majority of deaths during the study were directly attributed to progressive disease (table 2 above). Deaths not due to progressive disease were infrequent and occurred with a similar incidence across the treatment arms (6/233 [2.6%] in Pl + Doc, 9/250 [3.6%] in Bv 7.5 + Doc, 5/247 [2.0%] in Bv 15 + Doc arms). No particular pattern or cluster of adverse events could be identified that led to these deaths and most deaths were due to single causes; two patients each died due to febrile neutropenia, respiratory failure, and septic shock. There was only one death due to gastrointestinal perforation.

Other Serious Adverse Events

More patients in the Bv + Doc arms (37% and 42%) had serious adverse events compared with those in the Pl + Doc arm (33%), the difference being mainly due to a higher incidence of events considered to be primarily docetaxel related in these arms (table 2). The individual events with the most notable increase in incidence in the Bv + Doc arms included febrile neutropenia (11.6% in Bv 7.5 + Doc and 14.6% in Bv 15 + Doc vs 9.4% in Pl + Doc), neutropenia (4.8% and 6.5% vs. 2.1%, respectively), and asthenia (2.0% and 1.2% vs 0%, respectively). Conversely, there were more cases of serious infection in the Pl + Doc arm (2.6%) compared with the Bv + Doc arms (0.8% and 0.4%)

Adverse Events of Special Interest

As expected, more patients treated with either dose of bevacizumab experienced one or more adverse events of special interest (all grades) (75% in Bv 7.5 + Doc and 78% in Bv 15 + Doc vs 60% in Pl + Doc) (table 2). This was mainly due to more patients in these two arms experiencing bleeding events, in particular mucocutaneous bleeding (epistaxis), and hypertension.

Overall, Grade 3-5 adverse events of special interest were more common in the Bv + Doc arms compared with Pl + Doc (table 4). Of these events, only neutropenia, febrile neutropenia, and hypertension were more frequent in at least one of the Bv + Doc arms compared with the Pl + Doc arm. There were no differences in the incidence of Grade 3-5 events between the two bevacizumab-containing arms, except for hypertension which was increased in the Bv 15 + Doc arm. Grade 3-5 thromboembolic events occurred more frequently in the Pl + Doc arm than in either of the two Bv + Doc arms.

Table 7 Overview of the Incidence of Grade 3-5 Adverse Events of Special Interest, Study BO17708 (Safety Population)

AE of special interest	Pl + Doc (N=233) No. (%)	Bv 7.5 + Doc (N=250) No. (%)	Bv 15 + Doc (N=247) No. (%)
All body systems	73 (31.3)	88 (35.2)	90 (36.4)
Neutropenia	40 (17.2)	49 (19.6)	49 (19.8)
Febrile neutropenia	28 (12.0)	38 (15.2)	41 (16.6)
Thromboembolic events	9 (3.9)	3 (1.2)	3 (1.2)
Venous thromboembolic events	8 (3.4)	3 (1.2)	3 (1.2)
Arterial thromboembolic events	1 (0.4)	-	-
Hypertension	3 (1.3)	1 (0.4)	8 (3.2)
All bleeding	2 (0.9)	3 (1.2)	3 (1.2)
Mucocutaneous bleeding	2 (0.9)	1 (0.4)	1 (0.4)
Pulmonary hemorrhage	-	-	1 (0.4)
Gastrointestinal perforation	2 (0.9)	1 (0.4)	2 (0.8)*
Abscess and fistula	1 (0.4)	2 (0.8)	1 (0.4)
Wound healing complication	2 (0.9)	1 (0.4)	1 (0.4)
Congestive heart failure	-	2 (0.8)	-
Proteinuria	-	-	1 (0.4)

Source: ae11tar345_s001

* Includes one patient with duodenal ulcer that resulted in ulcer perforation

Laboratory Parameters

No new safety signals associated with bevacizumab treatment were identified from the laboratory test results in study BO17708. Most of the post-baseline abnormalities for laboratory parameters were Grade 1-2. As expected from the adverse events reported in the study, the only remarkable laboratory abnormality was Grade 3-4 low neutrophil count, reported with a similar frequency across the treatment arms.

Vital Signs

Mean diastolic blood pressure values did not change markedly from baseline in patients in Pl + Doc and Bv 7.5 + Doc arms. A slight decrease in mean systolic blood pressure was reported in the Pl + Doc arm (- 4 mmHg), and slight increases in both mean systolic (+ 4 mmHg) and mean diastolic (+ 4 mmHg) blood pressure were seen in the Bv 15 + Doc arm.

No clinically relevant changes from pre-treatment baseline values were observed in any treatment arm for body temperature, pulse, weight or ECG parameters.

The analyses of laboratory findings and vital signs did not show any unexpected safety signals in patients treated with bevacizumab in combination with docetaxel. The treatment is associated with a known degree of toxicity which is to a large extent manageable. With the measures available it would not seem to have and adverse effect of the QoL of patients compared to patients treated with docetaxel alone, but it does not seem to improve QoL either.

Safety in special populations
No new information on safety of bevacizumab in special populations was presented. Considering the large amount of data available on bevacizumab for other indications this is acceptable.

Immunological events
No information is provided. According to the large database of post-marketing adverse events, immune system disorders are rare. It is therefore acceptable that immunological events were not reported in the present application.

Discontinuation due to AES
The addition of bevacizumab to docetaxel did not lead to more patients discontinuing bevacizumab/placebo due to adverse events. Indeed, fewer patients in the Bv 7.5 + Doc arm (8.0%) discontinued bevacizumab due to adverse events than in either the Bv 15 + Doc (11.7%) or the Pl + Doc (11.2%) arms. There was no marked imbalance between the treatment arms with respect to the type and frequency of individual adverse events leading to bevacizumab discontinuation and most events in all treatment arms occurred in one to two patients only, the most common being asthenia, pulmonary embolism, diarrhoea, gastrointestinal haemorrhage, hypertension, and febrile neutropenia.

The most common adverse events leading to withdrawal (≥ 1% of patients) of any treatment component were:

- fatigue (Pl + Doc: 1.7%; Bv 7.5 + Doc: 2.4%; Bv 15 + Doc: 1.6%)
- asthenia (1.7%; 0.8%; 2.0%)
- peripheral oedema (2.1%; 0.4%; 0.4%)
- nail toxicity (1.3%; 1.6%; 1.2%)
- nail disorder (0.4%; 0.8%; 2.4%)
- peripheral sensory neuropathy (1.7%; 0.8%; 0.8%)
- pleural effusion (0.4%; 1.2%; 0.4%)
- febrile neutropenia (1.3%; 0.8%; 0%)
- hypertension (0%; 0%; 1.2%)
- myalgia (0.4%; 0.4%; 1.2%)
- hypersensitivity (0%; 0%; 1.2%).

No marked differences were observed between the treatment arms.

Risk Management Plan
The applicant has submitted a Risk Management Plan in the initial application. The RMP Version 5.0 is written in accordance with the current guidelines, and replaces RMP Version 4.0 dated 16 July 2007. This RMP summarizes the important identified and potential risks of the clinical use of bevacizumab in Genentech- and Roche-sponsored studies and experience from the post-marketing setting after initial approval in the US (26 February 2004) and the EU (12 January 2005).

No new safety concerns specific for the applied combination (Avastin in combination with taxane-based chemotherapy) have been identified. However, the RMP has been updated with safety information for bevacizumab in general, with pulmonary hypertension and microangiopathic haemolytic anaemia (MAHA) as newly identified safety concerns. Long-term effects of bevacizumab when used in the paediatric population are also included as missing information.

The RMP has been updated with new information from study BO17708, and additional updates include these major changes:

- Implement recommendations of the PDCO during their review of the paediatric investigation plan
- A report on CNS metastases
- Availability of new drug safety reports on cardiac arrhythmia, intravitreal use, renal failure and proteinuria, MAHA, termination of BO17934 (AVASQ).

The overall position is that the RMP is considered adequate provided some issues are further discussed and updated. A RMP rev. 6.0 is currently ongoing for evaluation in variation II/28.

Annex II of the product information has been updated to reflect the new version number of 5.0.

3 Discussion

In general, the patient population in this study was similar to that enrolled in study E2100 (bevacizumab and paclitaxel); the only slight differences in the inclusion / exclusion criteria between the two studies were the time allowed since completion of last previous neo-adjuvant / adjuvant chemotherapy prior to randomization (6 months in study BO17708 vs. 3 weeks in study E2100), in liver function tests (within normal ranges in study BO17708 vs. up to 1.5 x ULN in study E2100), and in levels of haemoglobin (lower limit of 9 g/dL in study BO17708 whereas severe anaemic patients were allowed in E2100). Although HER2-positive patients were allowed to enter study E2100 if they had failed trastuzumab, these were excluded from study BO17708. However, those patients only comprised 2.2 % of patients in E2100, so the populations of the two studies would seem to be largely comparable.

As is evident from the results with regard to the primary endpoint PFS there are marked differences in the results of the two studies, even when they are analysed in exactly the same manner. The hazard ratio in the E2100 study is significantly lower than the hazard ratio in the BO17708 study, and the difference in median PFS is markedly larger in the E2100 study. One cannot help suspecting that the lack of blinding in the E2100 study may have resulted in bias and a spuriously large difference in favour of the bevacizumab arm of the study. However, some of the differences between the E2100 study and the BO17708 study may be attributed to docetaxel being more active than paclitaxel, and to docetaxel having in itself more powerful antiangiogenic properties than paclitaxel. Thus, the effect of bevacizumab in patients treated with docetaxel may be more modest that than in patients treated with paclitaxel.

More patients were withdrawn from placebo/bevacizumab in the Pl + Doc arm (76%) than in the Bv 7.5 + Doc and Bv 15 + Doc arms (71% and 70%, respectively). This was mainly due to a greater number of patients in the Pl + Doc arm being withdrawn because of insufficient therapeutic response. Similarly, more patients in the Pl + Doc arm (55%) than in the Bv 7.5 + Doc and Bv 15 + Doc arms (53% and 48%, respectively) were withdrawn from docetaxel treatment, mainly due to insufficient therapeutic response. About 20 % of patients in all three arms stopped treatment prematurely due to violation of selection criteria at entry, adverse events, withdrawal of consent, or administrative/other reasons. This is a fairly high percentage, although it seems to be equally distributed between the treatment arms. About 50 % of patients were withdrawn from treatment before completion because of insufficient therapeutic response. These 50% of patients were considered as treatment failures. This again is a high percentage. All patients are sufficiently accounted for.

PFS was the primary endpoint in trial BO17708, the study was not powered for overall survival. The focus of the discussion will be on the bevacizumab 15 mg/kg q3w does which was consistently associated with better primary and secondary efficacy outcomes with similar safety compared to the 7.5 mg/kg q3w. This is in line with the posology approved for the treatment of first line metastatic breast cancer in combination with paclitaxel.

In the updated analysis (cut-off September 2008) a statistically significant improvement of two months in PFS is observed. The major concern of the CHMP was lack of evidence to prove that the prolongation in PFS with the addition of bevacizumab to docetaxel for the first-line treatment of patients with metastatic and/or locally recurrent breast cancer is of significant clinical benefit for the patients as it was not unambiguously supported by OS data. The CHMP recommended that the above question should be discussed at a SAG-oncology meeting.

3. 1 SAG-Oncology meeting on 7 May 2009

CHMP question: Does the SAG believe that the modest prolongation in PFS in the absence of any trend for Overall Survival improvement observed with the addition of bevacizumab to docetaxel for the first-line treatment of patients with metastatic and/or locally recurrent breast cancer is of significant clinical benefit for the patients?

The SAG agreed that the effect observed in terms of PFS could be considered to be clinically significant, provided that sufficient supportive data are available from important secondary endpoints, particularly overall survival. The SAG had different views as to whether the supportive data were sufficient or not.

1. According to some experts, it is important to weigh the urgency to license this indication, taking into account the availability of other agents and regimens, against ensuring that overall survival is ultimately not compromised. The overall survival analyses presented were based on less than 40% of the events. The data were too immature to rule out an important detriment in overall survival with adequate power. Although the hazard ratio was close to 1, a high number of censored observations and possibly crossing hazards towards the end of the observation period raised concerns. In conclusion, more mature overall survival data (for example with 50% or more events and adequate duration of follow-up) must be available before granting the extension of the indication to this combination.
2. According to an opposing view, although acknowledging that the data were immature, the overall survival did not pose particular concerns. The objective response rate was considered to be very high reflecting a high level of antitumour activity. Although it was difficult to conclude on the results about quality of life due to the missing data, there were no signs that the combination was associated with important worsening in quality of life. According to this view, the available data were considered sufficient to support the extension of the indication provided that more mature data for overall survival would be submitted as follow-up measure.

The SAG discussed the design and results of the trial in terms of dose selection. The rationale for a three-arm trial with two doses of bevacizumab remains unclear. Apart from visual exploration, there is no conclusive evidence of a difference between the two doses in terms of important clinical endpoints. Thus, discarding the lower dose based on the available data does not seem justified.

The holder of the marketing authorisation indicated that there are a number of biomarker analyses, including genotyping that are to be conducted in the near future. The SAG commented that such analyses are valuable and the results of these analyses should be submitted and assessed in order to better define the target population in the approved indications.

The SAG discussed the apparent differences observed with paclitaxel and docetaxel, in combination with bevacizumab. It has been reported that different cytotoxic agents may interact differently with antiangiogenic drugs (Shaked et al., 2008). The proposed indication that is currently for combination with taxanes should be limited reflect the taxanes actually studied because the results observed with one taxane cannot be easily extrapolated to other agents in this class.

3. 2. CHMP discussion and Oral Explanation

The Oral Explanation with the MAH focused on the following issues:

1) Is the modest PFS prolongation observed in Study BO17708 of clinical relevance to patients?

Following the unanimous agreement at the SAG meeting and extensive discussion among the CHMP, the effect observed in terms of PFS could be considered to be clinically significant.

2) The OS Kaplan Meier plot: the curves seem to cross at 24 months which remains a concern. A possible detrimental effect of bevacizumab can not be excluded. Please give your view and elaborate.

It can be agreed that no dentrimental effect on overall survival is suspected, based on HR of 0.94. The 1-year survival is slightly superior in the bevacizumab arm and for the first 15 months (the time period when data can be considered robust) the HR for survival is 0.75.

The overall survival analyses are and will always be confounded by the following factors:

- patients are receiving bevacizumab additionally in the second line setting
- placebo patients crossing over to bevacizumab before disease progression (allowed after the primary study results were made public)
- use of subsequent lines of therapy at discretion of investigator and uncontrolled by protocol

These issues validate the choice of PFS as primary endpoint in this study.

3) Preclinical data published earlier this year, although on other classes of antiangiogenetic treatment, indicate that long term treatment with inhibitors of the angiogenesis may in fact stimulate tumour growth. The CHMP would therefore like to have more information on the proportion of patients that progressed due to progression of the primary tumour versus progression due to new metastases and time to new lesions in the different treatment arms.

Two publications, Paez-Ribez et al. and Ebos et al. report in Cancer Cell that experimental models of transgenic or immunosuppressed mice transplanted with various tumour cell lines demonstrate increased invasiveness and metastatic spread when exposed to anti-angiogenic therapy with a tyrosine kinase inhibitor, sunitinib or VEGF receptor antibody. The studies were carried out using single agent treatment. In study BO17708 there were fewer patients with disease progression due to new lesions in the bevacizumab arms. There has been no evidence of accelerated progression or excess mortality following bevacizumab discontinuation as demonstrated in clinical data from 5 placebo controlled phase III trials comprising more than 4200 patients.

Following this discussion the CHMP requested the MAH to provide updated survival results since the latest cut-off (September 2008 – April 2009) without censoring for cross-over

3. 3. Updated Survival results

The trial was not powered for OS, but a more mature analysis of OS was pre-planned when all patients enrolled in the study had been followed for at minimum of 24 months.

At the time of the data cut-off in April 2009, 342 patients (46.5%) had died:
108 (44.8%) in the placebo+doxetaxel arm,
118 (47.6%) in the Bv7.5+docetaxel arm and
116 (47.0%) in the Bv15+docetaxel arm, respectively.

The median OS is now >30 months in every treatment group, but the estimates are still unreliable due to a lot of censoring after month 24.

In the *unstratified* analysis, the HR was:
1.03 (95% CI: 0.79; 1.33) in the bv15-docetaxel group compared to placebo-docetaxel
1.05 (95% CI: 0.81; 1.36) in the bv7.5-docetaxel group compared to placebo-docetaxel.

In a *stratified* analysis (by region, prior adjuvant/neo-adjuvant taxane/time to relapse since last dose of adjuvant/ neo-adjuvant chemotherapy, measurable disease, hormone receptor status), the HR was:
1.00 (95% CI: 0.76; 1.32) in the bv15-docetaxel group compared to placebo-docetaxel
1.10 (95% CI: 0.84; 1.45) in the bv7.5-docetaxel group compared to placebo-docetaxel.

The results indicate that there's no significant difference in OS between the treatment groups.
In the updated analysis, the available results are reliable and mature for the time period up to 24 months. At the time of the data cut-off in April 2009, 342 patients (46.5%) had died.
The Kaplan Meier curves now seem to meet around 22-24 months after which the curves are unreliable due to a large amount of censoring.
No significant difference in OS was observed between the high-dose bevacizumab arm and the placebo-arm (in both unstratified and stratified analyses), and specifically no detrimental effect on OS was noted after the addition of bevacizumab to docetaxel.

Presumably, it will be impossible to demonstrate a potential benefit of bevacizumab in combination with docetaxel on OS in mBC due to confounding effect of cross-over from the placebo group to bevacizumab upon progression and plus the availability of several 2nd and 3rd line therapies. (102 patients in the placebo arm received bevacizumab post progression)

4. Overall Conclusion and Benefit – Risk assessment

The present application is for an extension of the previously approved indication for the combination of bevacizumab and paclitaxel to an indication for the combination of bevacizumab and taxanes in general. The present application must therefore be seen in the context of the evidence from both the previous and the present applications. As stated above, there are differences between the results of the pivotal study for the approved indication (E2100) and for the present application (BO17708). Some of the differences have been plausibly explained by differences in methodology and possible differences in the performance of the two taxanes. The consultation with the SAG-O revealed that docetaxel and paclitaxel are considered to behave differently and they are not "inter-changeable": The synergy is probably largest with the combination of paclitaxel and bevacizumab, whereas docetaxel is more active than paclitaxel as single-agent. It should be up to the treating physician to choose which taxane to use according to knowledge of previous therapies, the related toxicities and the most optimal schedule for the patient.

Benefits

The primary endpoint was PFS. Regarding PFS there are some data that could affect the interpretation of the results: Only 80 % of the patients had measurable disease, the study was blinded but the investigators had knowledge on the doses which maybe could lead to bias. Furthermore, after the study became public, patients in the placebo arm were given the opportunity to cross over to bevacizumab.

The pivotal study BO17708 showed a statistically significant advantage for the combination of bevacizumab (at both dose levels) and docetaxel with regard to PFS. With the updated analyses presented, the difference was modest, with a median prolongation of PFS of 2 months for the patients in the high dose bevacizumab arm compared to the control arm. With the updated analyses, the improvement in PFS was seen at a follow-up for up to 18 months. This increased improvement in PFS with the updated analyses can be regarded as clinically relevant.

The benefits in terms of secondary endpoints were as follows: The OR was 64% in the high-dose bevacizumab arm compared to 46% in the placebo arm. The median duration of response was only slightly longer in the high-dose bevacizumab arm (8.5 months) than in the placebo arm (6.9 months). A modest difference in Time to Treatment Failure (7.9 months versus 6.3 months) was noted.

No significant difference in OS was found. In the updated analysis as of June 2009, the available results are reliable and mature for the time period up to 24 months. At the time of the data cut-off in April 2009, 342 patients (46.5%) had died. The Kaplan Meier curves now seem to meet around 22-24 months after which the curves are unreliable due to a large amount of censoring. No significant difference in OS was observed between the high-dose bevacizumab arm and the placebo-arm (in both unstratified and stratified analyses), and no detrimental effect on OS was noted after the addition of bevacizumab to docetaxel. But taking into consideration the cross over from the placebo group to bevacizumab upon progression + the availability of other 2nd and 3rd line therapies demonstrating a benefit in overall survival is no expected.

The SAG-O considered a median increase in PFS of 2 months to be of clinical benefit to the patients, but concern over the (immature) OS data were raised as the tail of the survival curves is still unreliable. All members of the SAG-O considered more follow-up regarding OS necessary.

QoL data are presented, but the only conclusion drawn is that the addition of bevacizumab does not lead to an overall deterioration in QoL scores. QoL scores are notoriously insensitive, so the information value from this analysis is limited.

Risks

The presented safety profile of the combination of docetaxel and bevacizumab does not add any new or unexpected toxicities. The AEs encountered with the combination are as would be expected from the present knowledge of the safety profile of the two drugs. Neutropenia, febrile neutropenia, hypertension, proteinuria, haemorrhage, congestive heart failure, gastrointestinal perforation, abscess and fistula, and wound healing problems are seen at an increased rate or severity with the combination. The individual incidence rates of these complications are not high and the incidence of grade 3-5 AEs for proteinuria, haemorrhage, congestive heart failure, gastrointestinal perforation, abscess and fistula and wound-healing complication, arterial or venous thromboembolic events are similar (defined as less than 1% difference or more frequent in the control arm) between bevacizumab 15 mg and the control arm. Nevertheless, they are significant, causing morbidity and serious risks, even of death.

Balance

The benefit of adding the high dose bevacizumab to docetaxel in patients with metastatic and/or locally recurrent breast cancer is very modest, amounting to a median prolongation of PFS of 2 months and with no effect on overall survival so far. Overall, PFS is considered a valid endpoint, and it is acknowledged that it is difficult to show an effect on OS at this stage as several 2nd and 3rd line therapies are available. However, it has been established that the proposed therapy does not have a harmful effect on OS. Taking into account that no patients with metastatic breast cancer are cured with the present treatment, an improvement in PFS but no difference in OS may be attractive if the quality of life is taken into consideration so that it outweighs the increased risk of adverse events. The quality of life data presented shows no deterioration in QoL.

As docetaxel and paclitaxel behave differently they are not considered “inter-changeable”. It is up to the treating physician to choose which taxane to use according to knowledge of previous therapies, the related toxicities and the most optimal schedule for the patient. Thus the proposed indication is restricted to paclitaxel or docetaxel specifically, instead of “taxane-based therapy” in general.

The increase in the incidence of adverse events with the combination compared to docetaxel alone is as expected from previous studies with other combinations of bevacizumab and cytotoxic drugs. The increase is fairly moderate, but nevertheless significant, causing morbidity and, in rare cases, even death.

HER2 status is not expected to impact the response of patients to bevacizumab treatment; therefore, the proposed indication is not restricted to HER2-negative patients only.

The overall B/R of bevacizumab in combination with docetaxel for the treatment of metastatic breast cancer is positive given that a clinical significant benefit in PFS has been observed and an acceptable safety profile was seen in these patients with incurable disease and consequentially this variation is recommended by a majority vote for a positive opinion for the following indication;

> ***Avastin in combination with <u>paclitaxel or docetaxel</u> is indicated for first-line treatment of patients with metastatic breast cancer. For further information as to HER2 status, please refer to section 5.1.***

The full and final OS data should be submitted post authorisation (expected to be available in Q4 2009)

Divergent opinions expressed by some CHMP members supported that:

- In study BO17708 Avastin in combination with docetaxel was compared with docetaxel plus placebo, as first-line treatment for patients with HER2-negative metastatic or locally recurrent

breast cancer who have not received prior chemotherapy for their metastatic disease. The estimated increase in median progression free survival of only 2 months when adding Avastin 15 mg/kg to docetaxel is considered to be of marginal clinical relevance.

- The marginal increase in progression free survival is not supported by any increase in overall survival.

- In light of the adverse events related to combination treatment a median increase in PFS alone of 2 months or less, without support from overall survival data, is seen as insufficient.

II. CONCLUSION

On 25 June 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.