London, 22 February 2007
Product name: **Avastin**
EMEA/H/C/582/II/08

SCIENTIFIC DISCUSSION

Extension of the indication to include Avastin in combination with paclitaxel for first-line treatment of patients with metastatic breast cancer.

1. Introduction

Avastin contains bevacizumab, a recombinant humanized IgG1 antibody that binds and inhibits VEGF-induced effects *in vitro* and *in vivo*. VEGF, an endothelial cell-specific mitogen, is a regulator of angiogenesis and is believed to play a major role in tumourgenesis. Bevacizumab blocks the binding of VEGF to its receptor, thereby inhibiting angiogenesis and tumour growth. Bevacizumab has been developed as a novel therapeutic for treating solid tumours, and has been authorised in EU in January 2005 for the treatment of colorectal carcinoma.

The MAH applied for the indication: "Avastin (bevacizumab) in combination with paclitaxel is indicated for first-line treatment of patients with locally recurrent or metastatic breast cancer". The recommended dose of Avastin is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg given once every 3 weeks as an intravenous infusion.

Breast cancer is the most common cancer in women worldwide and the highest rate of occurrence is in Western Europe and North America. It has been estimated that in the year 2000, there were 350 000 new breast cancer cases in Europe and that 130 000 women died as a result of breast cancer. Breast cancer is responsible for 26.5% of all new cancer cases amongst women in Europe and 17.5% of all cancer deaths.

The median survival for patients with metastases at diagnosis is around 2-3 years with <20% still alive at 5 years. For women who are not candidates for hormonal therapy, cytotoxic chemotherapy is the treatment of choice for metastatic disease or locally recurrent disease that is not amenable to curative therapy. A variety of cytotoxic drugs are active in breast cancer, including anthracyclines, taxanes, alkylating agents, vinca alkaloids and anti-metabolites, such as 5-fluorouracil, capecitabine or methotrexate.

Paclitaxel is licensed for and widely used in the treatment of patients with breast cancer, in both the metastatic and adjuvant setting, due to its good activity and acceptable safety profile. It has also been successfully combined with monoclonal antibody therapy in the treatment of patients with HER2 (human epidermal growth factor receptor type 2)-positive breast cancer in both settings. Thus, paclitaxel is a logical choice for combining with bevacizumab, from a clinical perspective. Non-clinical data also support the combination of bevacizumab and a taxane (paclitaxel or docetaxel) since bevacizumab shows synergistic activity with docetaxel, as assessed by endothelial cell proliferation and tubule formation, in vitro.

2. Clinical aspects

The clinical development program for bevacizumab in metastatic breast cancer consists of one large pivotal phase III trial of bevacizumab in combination with paclitaxel versus paclitaxel alone (study E2100) including 722 patients, and two supportive studies. The first supportive study was a phase I/II study with three different doses of bevacizumab monotherapy (study AVF0776g) including 75 patients. The second was a phase III study of bevacizumab in combination with capecitabine versus capecitabine alone (study AVF2119g) including 462 patients.

The pivotal study E2100 was conducted according to the Eastern Cooperative Oncology Group (ECOG) standard operating procedures ((ECOG Policy and Procedures Manual, Version 4 (November 2000) and Version 5 (March 2003)), and in accordance with all Department of Health and Human Services, Office of Human Research Protections, and U.S. Food and Drug Administration (FDA) regulations regarding the conduct of human research that gave their origins in the Declaration of Helsinki. The AVF2119g study and theAVF0776g study were performed in concordance with current standards for the design, conduct, and analysis of clinical research, including GCP and all region-specific requirements.

2.1 Clinical Pharmacology

The clinical pharmacology program comprised 10 studies with bevacizumab, which enrolled patients with a variety of tumor types, and evaluated a variety of dosing regimens. Nine of these studies were submitted previously in the original Marketing Authorisation Application (MAA) submission for colorectal cancer.
Three of these were trials of bevacizumab monotherapy, five were combination trials of bevacizumab with various cytotoxic chemotherapy regimens, and one was a trial of preoperative bevacizumab which provided pharmacodynamic data only. One additional pharmacokinetic study is included with this submission – a trial of bevacizumab in combination with erlotinib in patients with non-small cell lung cancer (NSCLC).

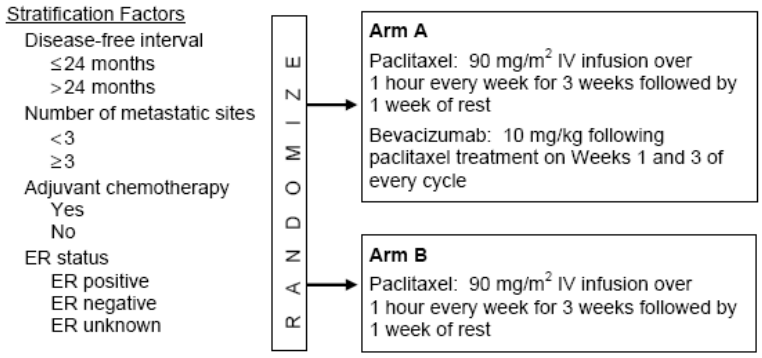
The effects of demographic, pathophysiological covariates and concomitant administration of chemotherapeutic agents, on the pharmacokinetics of bevacizumab have also been assessed using population pharmacokinetic (PK) analysis of data from the eight originally submitted studies.

2.2 Clinical Efficacy

One large, randomized open-label **pivotal phase III trial (E2100)** of paclitaxel versus paclitaxel plus bevacizumab (rhuMAb VEGF) as first-line therapy for locally recurrent or metastatic breast cancer including 722 patients was submitted to support the claimed indication. 722 patients were randomized (1:1) to paclitaxel at a dose of 90 mg/m^2 weekly for 3 weeks followed by 1 week of rest with or without bevacizumab at a dose of 10 mg/kg every two weeks. 354 patients were randomized to receive paclitaxel alone and 368 patients were randomized to receive paclitaxel plus bevacizumab. The primary endpoint of the trial was progression-free survival (PFS).

The applicant has provided justification for the 10mg/kg every two week dosage. The overall exposure is similar when bevacizumab is given at a dose of 5 mg/kg/wk, either as 10 mg/kg/2w or as 15 mg/kg/3w. A commitment to provide results from an ongoing study BO17708 as soon as it is available has also been given.

Study scheme



The pivotal study comprised patients with recurrent and metastatic breast cancer who have not over-expressed HER2 or had received prior therapy with Herceptin. Patients with unknown HER2 status were not eligible unless Herceptin-based therapy was considered inappropriate or not indicated. Virtually all patients entered in the pivotal study had disease recurrence after initial local treatment plus some form of adjuvant treatment (radiotherapy, antihormonal treatment, chemotherapy). Some had also received antihormonal treatment or radiotherapy for a previous recurrence.
Only a very small number (13) had locally recurrent breast cancer, which is to be expected as isolated loco-regional recurrence is less common, and some patients with loco-regional recurrence only will be treated less aggressively, either with local treatment or just anti-hormonal treatment. However, some of these patients will be candidates for more aggressive treatment, and there is no indication that the response of the disease in this situation is qualitatively different from the response in otherwise similar patients where the disease has metastasised outside the chest wall and local lymph node regions.

However, to reflect the small number of patients with locally recurrent breast cancer only in this study, the initially proposed indication has been revised to target the metastatic breast cancer population.

The **two supportive studies** were:
An open-label, multidose, multicenter **phase I/II study (AVF0776g)** to evaluate the safety, efficacy and pharmacokinetics of recombinant humanized monoclonal anti-VEGF antibody (rhuMAb VEGF) as monotherapy in patients with relapsed metastatic breast cancer. 75 patients with previously-treated metastatic breast cancer received 3, 10 or 20 mg/kg bevacizumab as monotherapy every two weeks

An open-label, multicenter, randomized **phase III trial (AVF2119g)** evaluating the efficacy, safety and pharmacokinetics of rhuMAb VEGF (bevacizumab), in combination with capecitabine chemotherapy versus capecitabine monotherapy, in patients with previously treated metastatic breast cancer. 462 patients were randomized (1:1) to capecitabine 2500 or 1875 mg/m^2/day for 2 weeks followed by a 1 week rest with or without bevacizumab 15 mg/kg every three weeks. 230 patients were randomized to receive capecitabine alone and 232 patients were randomized to receive capecitabine plus bevacizumab.

The two supportive studies did not test the proposed indication, and therefore contributed only to the safety evaluation. Also, the differences in the baseline characteristics in study AVF0776g and E2100 make the comparison between the studies difficult.

The primary objective of the pivotal Phase III study E2100 was:

- To evaluate the efficacy of paclitaxel in combination with bevacizumab compared with paclitaxel alone, in patients with chemotherapy-naïve locally recurrent or metastatic breast cancer as measured by PFS (originally it was time to treatment failure, but this was changed by an amendment requested by the FDA).

The secondary objectives were:

- To evaluate the objective response rate, duration of response, and OS in patients with chemotherapy-naïve locally recurrent or metastatic breast cancer treated with paclitaxel in combination with bevacizumab compared with paclitaxel alone.
- To evaluate the toxicity of paclitaxel in combination with bevacizumab compared with paclitaxel alone.
- To compare the quality of life (Functional Assessment of Cancer therapy – Breast (FACT-B)) of patients treated with paclitaxel to that of the combination of paclitaxel plus bevacizumab as first-line therapy for MBC.

Other objectives were:

- To examine the effect of missing tumor assessments, non-protocol therapy, and early discontinuation on the primary PFS results.
- To examine the effects of demographic and baseline prognostic characteristics on PFS, OS, and objective response rate. The characteristics include disease-free interval, number of metastatic sites, adjuvant chemotherapy, estrogen receptor status, ECOG performance status, age, sex, race, baseline sum of the longest diameters of all target lesions, and HER2 expression status by immunohistochemistry.
- To compare time to treatment failure of patients treated with the combination of paclitaxel plus bevacizumab to that of paclitaxel alone.

Disease progression and tumor response were assessed by the investigator and confirmed by ECOG (based on an unblinded review of data submitted by the investigator), according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

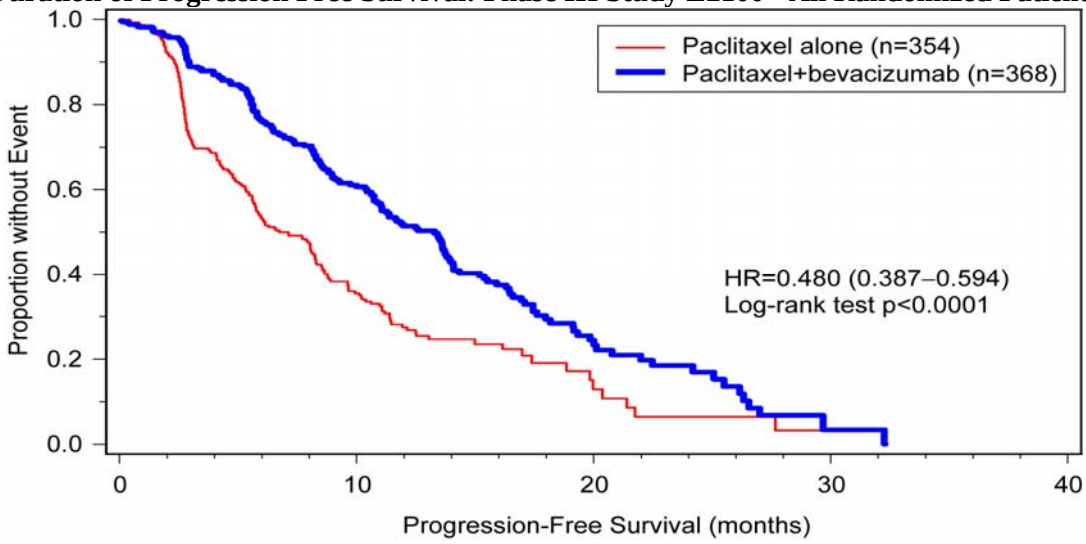
Primary endpoint

- **Progression free survival (PFS)**

The stratified analysis of the primary endpoint of duration of PFS for all randomized patients demonstrated a clinically and statistically significant increase in the median duration of PFS from 6.7 to 13.3 months among patients in the paclitaxel plus bevacizumab arm compared with those in the

paclitaxel alone arm (p<0.0001). The stratified hazard ratio for the paclitaxel plus bevacizumab arm relative to the paclitaxel alone arm was 0.48 (95% CI: 0.39, 0.59).
The Kaplan-Meier curves for the duration of PFS are shown in the following figure:

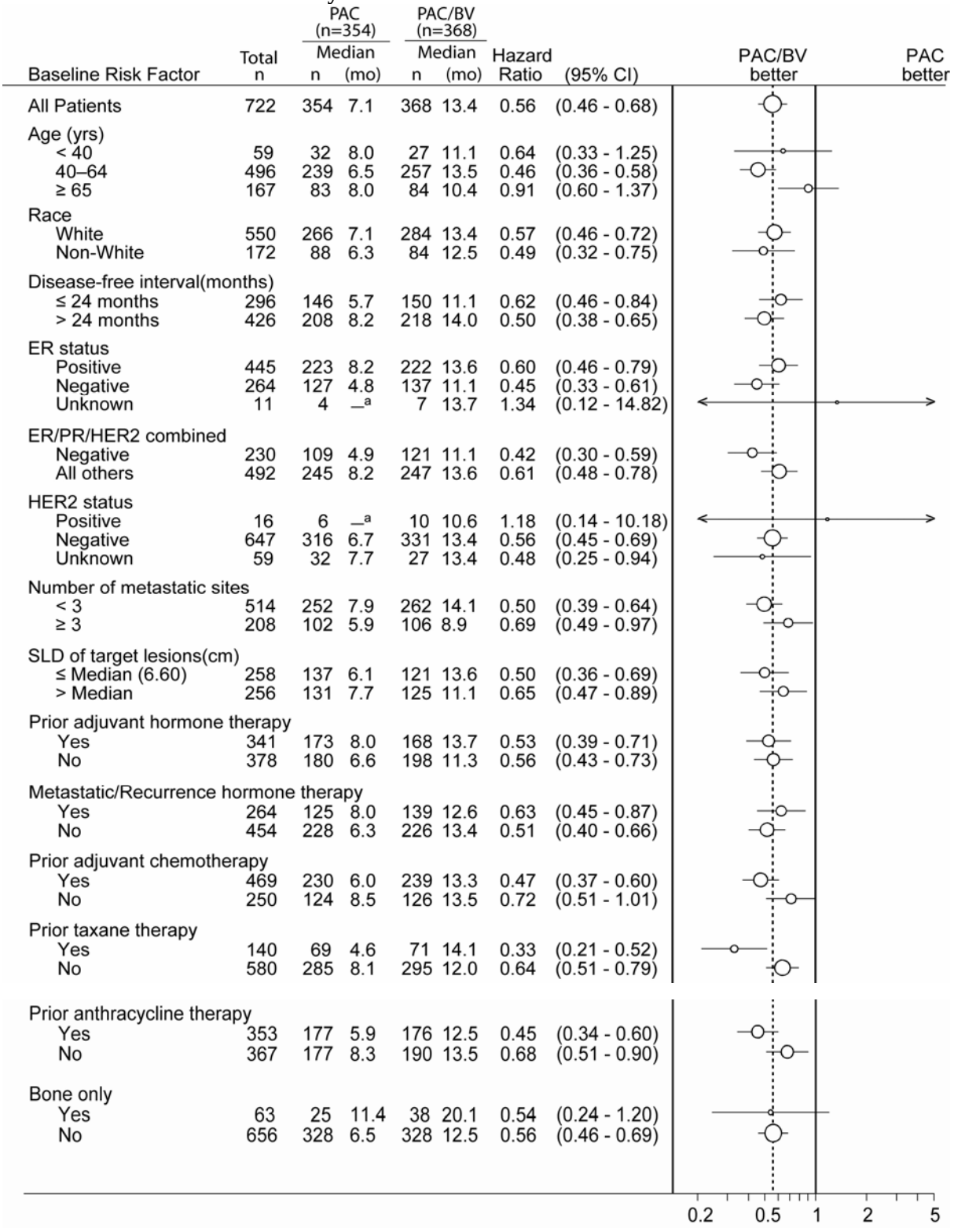
Duration of Progression Free Survival: Phase III Study E2100 - All Randomized Patients



Comparisons of results in subgroups were performed. Subgroups included those defined by the four stratification variables (disease-free interval, number of metastatic sites, prior receipt of adjuvant chemotherapy, and ER status) as well as demographic and baseline characteristics, such as age (<40, 40–64, ≥65 years), race (White, non-White), baseline sum of the longest diameters of all target lesions, and HER2 expression status by FISH and IHC. Other characteristics considered but not pre-specified for subgroup analysis included prior adjuvant hormone therapy, prior hormone therapy for locally recurrent or MBC, and prior taxane or anthracycline therapy.

The reduction in the risk of progression or death in clinically important patient subgroups was generally consistent with the results seen in the overall analysis. There was a consistent increase in PFS observed across all subgroups of patients in the paclitaxel + bevacizumab arm, including those with a poor prognosis or response to treatment. The benefit of adding bevacizumab to paclitaxel was seen irrespective of prior therapy (anthracyclines or taxanes), disease-free interval, sites of disease or tumor burden quantified by size of target lesions in patients with measurable disease, or hormone receptor status, including patients with negative results on ER, PR and HER2 receptor assays (i.e. triple-negative patients). It is however noted that the extent of the difference in progression-free survival was less pronounced in patients ≥ 65 years, with a HR of 0.91.

Duration of Progression-Free Survival by Baseline Characteristics:
Study E2100 – All Randomized Patients



CI = confidence interval; PAC = paclitaxel; PAC/BV = paclitaxel plus bevacizumab; SLD = sum of longest diameter.
HER2 is positive if "amplified" by FISH or "3+" by IHC per protocol. Median PFS was estimated from Kaplan-Meier curves. Hazard ratio relative to PAC was estimated by Cox regression. Unstratified hazard ratio is displayed. [a] Median not available because of 0 or only 1 event.

In addition to determining the treatment effect across a number of subgroups, proportional hazards regression was applied to estimate the effect of bevacizumab after adjusting for important prognostic factors for PFS. The final model for duration of PFS included the following: treatment, disease-free interval, number of metastatic sites, and ER status, see following table.

Progression-Free Survival by Baseline Risk Factor: Study E2100

Baseline Risk Factor	DF	Parameter Estimates	SE	Hazard Ratio (95% CI)	p-value
Treatment					
Pac (reference)					
Pac + Bv	1	–0.61	0.10	0.54 (0.45, 0.66)	<0.0001
Disease-free interval (months)					
≤24 months (reference)					
>24 months	1	–0.25	0.10	0.78 (0.64, 0.95)	0.0133
Number of metastatic sites					
<3 (reference)					
≥3	1	0.47	0.11	1.60 (1.30, 1.96)	<0.0001
ER status					
Negative (reference)					
Positive	1	–0.43	0.10	0.65 (0.53, 0.80)	0.0001
Unknown	1	–0.71	0.46	0.49 (0.20, 1.20)	

CI = confidence interval; DF = degree of freedom; ER = estrogen receptor; Pac = paclitaxel; Pac + Bv = paclitaxel + bevacizumab; SE = standard error.

After adjusting for these factors, a strong benefit remained for treatment with paclitaxel plus bevacizumab. The adjusted hazard ratio indicates an approximately 46% reduction in the hazard of progressive disease or death among patients who received paclitaxel plus bevacizumab treatment compared with those who received paclitaxel alone

Secondary endpoints

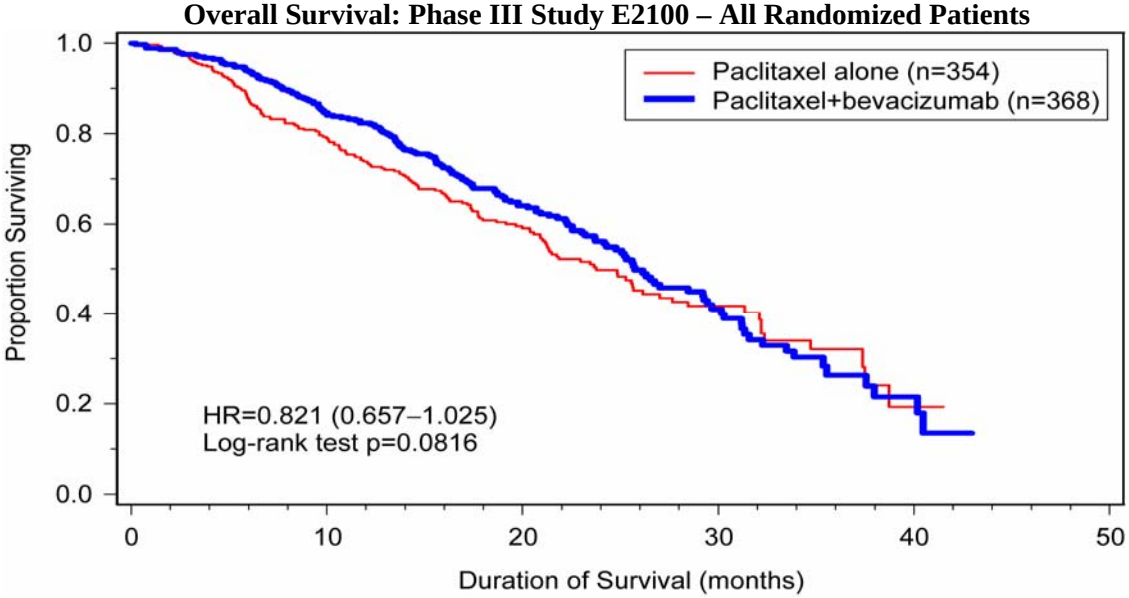
- **Overall survival**

In the E2100 trial the median duration of follow-up for OS is 22.6 and 22.3 months for the paclitaxel and paclitaxel plus bevacizumab arms, respectively. At the time of the analysis, a total of 337 patients had died; 169 patients in the paclitaxel plus bevacizumab arm and 168 patients in the paclitaxel alone arm. This represents 70% of the 481 deaths required for the final analysis. The stratified analysis of OS for all patients demonstrated a longer median OS among patients in the paclitaxel plus bevacizumab arm compared with those in the paclitaxel alone arm. Median OS was 25.7 months in the paclitaxel plus bevacizumab arm versus 23.8 months in the paclitaxel alone arm. The stratified hazard ratio for death for the paclitaxel plus bevacizumab arm relative to the paclitaxel alone arm was 0.82 (95% CI: 0.66, 1.03; p = 0.082). There was thus no significant difference between the two treatment arms with regard to overall survival. Kaplan-Meier curves for OS are shown in the following figure. However, based on the number of patients at risk, this analysis was considered preliminary. Mature overall survival data is anticipated by 4Q 2007.

A significantly better survival rate in the paclitaxel plus bevacizumab arm than in the paclitaxel alone arm was seen at 1-year, with 82.3% of patients still alive versus 73.8% (p-value 0.007), respectively (based on Kaplan-Meier estimates). However, 1-year overall survival was not a pre-specified endpoint. All patients except for 26 (7%) in each arm were reported to have been followed for at least 1 year. With limited follow-up at two years, the survival rate is 38.6% in the paclitaxel plus bevacizumab and 36.4% in the paclitaxel alone arm.

Crossover to bevacizumab after progression for patients in the paclitaxel alone arm was not offered as part of the protocol, nor were patients in the paclitaxel plus bevacizumab arm offered additional bevacizumab after progression. However, no information was collected regarding subsequent therapy after disease progression was determined for any patient. Thus, the impact of post-progression therapy, including bevacizumab, particularly for the patients in the paclitaxel alone arm, on OS was not discernable. Bevacizumab became commercially available in the US and elsewhere during the study, and thus crossover may have occurred. Lack of such information makes interpretation of the overall survival data difficult.

Overall Survival: Phase III Study E2100 – All Randomized Patients



- **Objective response**

In the E2100 study, among patients with measurable disease at baseline (268 patients [75.7%] in the paclitaxel alone arm and 246 [66.8%] in the paclitaxel plus bevacizumab arm), the objective response rate was statistically significantly higher ($p < 0.0001$) in the paclitaxel plus bevacizumab arm (36.2%) compared with the paclitaxel alone arm (16.4%) – an increase of 19.8%. Although the majority of objective responses reported were partial responses, a greater percentage of patients in the paclitaxel plus bevacizumab arm (15/89; 17%) achieved a complete response compared to patients in the paclitaxel alone arm (5/44; 11%) and the absolute percentage of patients with a complete response was higher in the paclitaxel plus bevacizumab arm (15/246, 6.1%) compared to the paclitaxel alone arm (5/268, 1.9%).

- **Duration of response**

In the E2100 study, among all randomized patients with an objective response, the duration of objective response was longer in the paclitaxel plus bevacizumab arm than in the paclitaxel alone arm. The median duration of response for the 86 patients with an objective response in the paclitaxel plus bevacizumab arm was 11.3 months versus 9.0 months for the 43 patients with an objective response in the paclitaxel alone arm. Because the determination of duration of objective response was based on a non-randomized subset of patients, formal hypothesis testing was not performed. However, the treatment arms were compared for descriptive purposes among patients with an objective response ($p=0.5197$ from the unstratified log-rank test).

- **Quality of life**

The FACT-B questionnaire used and presented for evaluation is a valid and recognized measure of quality of life (QoL) in patients with breast cancer. As in so many QoL studies the treatment of missing data is the problem. A significant number of questionnaires were missing at week 17 and 33. Hence, data from these points in time could not be included. To account for missing data, the MAH conducted analyses of data using a number of imputation rules for missing data. In an anaylsis specified in SAP, where the missing scores for patients who died or had progressive disease prior were taken as zero (i.e. worst QoL score), an improvement in QoL was seen in the combination arm compared with control. The results of analyses using other imputation rules also showed a trend towards a better QoL with bevacizumab treatment even with the most conservative imputation method. However, the fact that QoL data were obtained in an open-label phase III trial (i.e. in an unblinded manner) makes any conclusions less reliable.

Summary of efficacy results in trials AVF0776g and AVF2119g

In the Phase I/II study AVF0776g, median time to progression was reported this was similar between the three doses of bevacizumab studied: 2.3, 2.5 and 2.3 months in the 3 mg/kg, 10 mg/kg and 20

mg/kg arms, respectively. Overall, objective tumor responses (complete or partial response) were documented in 7 of 75 (9.3%) patients and confirmed in 5 (6.7%) patients. Of those patients with a confirmed response, one (6%) patient each treated with 3 mg/kg and 20 mg/kg had a partial response, two patients (5%) treated with 10 mg/kg had a partial response and one patient (2%) had a complete response. The two unconfirmed responses were both partial responses and occurred in the 10 mg/kg group. Stable disease or better at the last tumor assessment after five months of treatment was seen in 12/75 (16%) of patients. Across all doses tested, the median duration of the five confirmed responses was 5.5 months, and the individual durations of response were 2.3, 3.1, 3.7 (censored), 5.6, and 13.7 months.

In study AVF2119g which was conducted in heavily pretreated patients, at the time of data cutoff 272 patients had experienced an event: 126 patients (54.7%) in the capecitabine alone arm and 146 patients (62.9%) in the bevacizumab plus capecitabine arm. The stratified efficacy analysis did not demonstrate a statistically significant effect of bevacizumab treatment on PFS. The median PFS was 4.2 months in the capecitabine alone arm and 4.9 months in the bevacizumab plus capecitabine arm; the hazard ratio relative to capecitabine alone was 0.98, indicating no significant treatment benefit..
In the AVF2119g study, the objective response rate was statistically significantly higher (p=0.001) in the bevacizumab plus capecitabine arm (46/232; 19.8%) than in the capecitabine alone arm (21/230; 9.1%) - an absolute increase of 10.7% and a more than doubling in relative terms. None of the responses were assessed as complete responses. The objective response rate by INV assessment was also statistically significantly higher (p=0.006) in the combination arm (30.2%) than in the capecitabine alone arm (19.1%), with a similar magnitude of effect (11.0% absolute difference). Nine of the objective responses by INV assessment were considered complete responses.
There was substantial censoring of duration of objective response: 51% of responders in the IRF/INV analysis and 45% of responders in the INV analysis had an ongoing response at the last tumor assessment before the data cutoff date. Although a significantly higher response rate was observed in the bevacizumab plus capecitabine arm than in the capecitabine alone arm (19.8% vs 9.1%), the median duration of objective response was shorter in the bevacizumab plus capecitabine arm, according to both the IRF/INV (4.96 vs 7.56 months) and INV assessments (4.96 vs 6.70 months).
Because this analysis is based on a non-randomized subset of patients, caution should be taken in comparing duration of objective response between the two arms. The additional responders in the bevacizumab plus capecitabine arm tended to have responses of short duration and the proportion of patients with responses longer than four months in duration was approximately equal in the two arms.

Overall conclusions on clinical efficacy

This application is based on two open–label, randomised, two arms, phase III studies and one un–controlled, single arm, phase II study which were conducted with patients with locally recurrent and metastatic breast cancer. The pivotal study (E2100) was conducted at 259 centres in the USA and compared bevacizumab 10 mg/kg/q2w and paclitaxel *vs.* paclitaxel alone. The treatment was given until disease progression or inability to tolerate investigational product. Crossover to bevacizumab after progression for patients in the paclitaxel alone arm was not offered as part of the protocol. The demographic and disease data were similar between the two treatment arms, and these data are considered as representative of patients with advanced breast cancer. However, only a small number (13 of 722 [1.8%]) of patients in this study had locally recurrent breast cancer and consequently the the initial proposed indication has been revised to target the metastatic breast cancer population.

The MAH has proposed 10mg/kg every two week dosage. It is agreed that the overall exposure is similar when bevacizumab is given at a dose of 5 mg/kg/wk, either as 10 mg/kg/2w or as 15 mg/kg/3w and the lack of comparative data of the currently authorised 5 mg/kg/2w dose versus the tested 10 mg/kg/2w dose can be justified.

The primary objective of this study was to assess whether bevacizumab plus paclitaxel improves progression–free survival compared with paclitaxel alone in subjects with locally recurrent or metastatic breast cancer. The secondary objectives were to evaluate the objective response rate, duration of response, overall survival, toxicity, quality of life in patients with chemotherapy–naive locally recurrent or metastatic breast cancer treated with paclitaxel in combination with bevacizumab compared with paclitaxel alone.

The pivotal study E2100 showed a significant prolongation of PFS from a median of 6.7 months with paclitaxel alone to a median of 13.3 months with paclitaxel plus bevacizumab. PFS was the primary endpoint of the trial. However, as the study was an open-label study with no blinding with regard to the assessment of response and progression parameters, a risk of bias in the evaluation of PFS cannot be excluded. An independent review of the data is ongoing with a planned submission by 4Q 2007.

There was no statistically significant improvement in OS, although the 1-year survival was significantly better in the paclitaxel plus bevacizumab arm. However, data are not yet mature enough for the final analysis of OS. Mature overall survival is expected by 4Q 2007 and will be provided as a post-approval committment.

QoL is stated as a secondary endpoint in the trial. The FACT-B questionnaire is a valid and recognized measure of quality of life in patients with breast cancer. As in so many QoL studies, the handling of missing data is problematic, and, together with the fact that QoL data were obtained in an open-label phase III trial (i.e. in an unblinded manner), makes any conclusions drawn from these analyses less reliable.

The comparison between the efficacy results from the pivotal study (E2100) and the two supportive studies (one phase III [AVF2119g] and one phase II [AVF0776g]) is difficult as there are different inclusion and exclusion criteria and different treatment regimes. In the Phase III study AVF2119g, efficacy and safety of bevacizumab when combined with capecitabine was compared with capecitabine alone in patients previously treated with both an anthracycline and a taxane, either in the adjuvant or metastatic setting. In this study no significant prolongation of PFS was observed. Although this study cannot be directly relevant to the present application the lack of effect when bevacizumab is used as add-on to capecitabine is being further explored by the MAH in a study recruiting less heavily pretreated patients with metastatic breast cancer.

2.3. Clinical safety

The overall evaluation of safety information for the proposed indication in locally recurrent or metastatic breast cancer (mBC) comes from the Phase III study, E2100, of bevacizumab in combination with paclitaxel as first-line therapy. In addition, safety information from the Phase II study, AVF0776g, of bevacizumab as monotherapy in patients with relapsed MBC and from the Phase III study, AVF2119g, of bevacizumab in combination with capecitabine in patients with previously treated mBC is also included. In total, 362 patients were exposed to bevacizumab in combination with paclitaxel, 75 to bevacizumab alone and 229 to bevacizumab in combination with capecitabine. Given the differences between the three studies in data collection and recording, as well as in the patient populations (specifically, exposure to prior therapy in the adjuvant and metastatic setting) and study designs (monotherapy versus combination with chemotherapy), pooling of the safety data from the three studies is not considered meaningful.

AEs were collected differently for each study. Study E2100 was conducted by the Eastern Cooperative Oncology Group (ECOG) and NCI-CTC Grade 3-5 non-hematological AEs and Grade 4 and 5 hematological AEs were reported on the ECOG Toxicity Form of the CRF.
For studies AVF0776g and AVF2119g, information on all AEs (all grades) was reported. In both studies, patients were evaluated for AEs at each study visit for the duration of their participation in the study. In study AVF0776g, patients discontinued from treatment because of disease progression were evaluated for safety four weeks after the last dose of bevacizumab. In study AVF2119g, patients discontinued from study treatment because of disease progression were evaluated 21 days after the last dose of bevacizumab or seven days after the last dose of capecitabine for patients randomized to capecitabine alone.

Due to the differences in collection of AEs between studies, safety evaluations in this summary document for study E2100 are based on AEs reported in the CRF Toxicity Form for cross-study comparisons. AEs reported to AdEERS are provided but only used to gain a more complete safety

profile of bevacizumab-treated patients. For study AVF2119g, safety evaluations are based on the period prior to disease progression, in which full safety data are available for both treatment arms.

The most common AEs in the three studies in mBC occurred in the body systems gastrointestinal disorders, and general disorders and administration site conditions. In these body systems, the most frequently reported AEs were nausea, vomiting and fatigue/asthenia. These AEs which are frequently associated with chemotherapy, but also occur with bevacizumab monotherapy, occurred with a similar frequency in the different treatment arms in each study. The addition of bevacizumab treatment did not appear to increase the frequency of these AEs in the combination arms, apart from a slight increase (< 5%) in the incidence of fatigue in study E2100, which may potentially be associated with longer treatment duration with paclitaxel in the combination arm.

The AEs that were increased in the combination arms of each study E2100 and AVF2119g (≥ 2% difference between treatment arms) have previously been identified as being associated with bevacizumab treatment. In study E2100 these AEs included hypertension (15.5% in the paclitaxel plus bevacizumab arm vs 1.4% in the paclitaxel arm) and proteinuria (3.0% vs. 0%). Peripheral sensory neuropathy was also increased in the combination arm (23.2% vs. 16.5%), although this difference in incidence between treatment arms is likely to have been due to the longer duration of treatment and greater cumulative dose of paclitaxel received by patients in the combination arm.

Serious adverse events and deaths
In study E2100, information regarding patient deaths was collected in at least one of the following three sources:
1. On the E2100 CRF Long-Term Follow-Up Form for both treatment arms
2. As NCI-CTC Grade 5 events on the E2100 CRF Toxicity Form for both treatment arms
3. As NCI-CTC Grade 5 events reported to NCI AdEERS for the paclitaxel plus bevacizumab arm only

A direct comparison of Grade 5 events across the treatment arms cannot be performed. In study E2100 in the paclitaxel plus bevacizumab arm, 13 patients had NCI-CTC Grade 5 events. In summary the Grade 5 AEs in study E2100 (CRF Toxicity Form only) and the AEs leading to death in study AVF2119g were mostly single events in different body systems with no obvious clustering or unifying features. There were no AEs leading to death in study AVF0776g.

The targeted AEs are more frequent in the patients treated with the combination with bevacizumab. They are not unexpected given the known toxicity profile of bevacizumab. Hypertension, proteinuria, arterial thromboembolic events, hemorrhage, congestive heart failure, gastrointestinal perforation, and wound healing problems are seen at an increased rate with the combination, whereas the neuropathy seems to be explained by the longer treatment in the combined arm. Although most of these complications are infrequent, seen only in 1-2 % of patients, they cause significant morbidity and may be lethal.

Discussion on clinical safety
Data from 1227 patients (E2100: 708 patients; AVF2119g: 444 patients; AVF0776g: 75 patients) who had received at least one full or partial dose of study medication were included in the safety analyses. Only the data from the pivotal E2100 study can provide information on the toxicity of the combination of paclitaxel and bevacizumab applied for. Only Grades 3-5 haematological and Grades 4-5 non-haematological AEs were reported, so less serious (but potentially still significant) AEs were not reported. Some events were reported through the NCI Adverse Event Expedited Reporting System, but only for patient in the paclitaxel plus bevacizumab arm, which makes comparisons between the combination and the paclitaxel only arm difficult.

The presented safety profile of the combination of paclitaxel 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. The most common serious adverse events that were ≥ 2% difference in incidence were: sensory neuropathy (16.5% *vs.* 23.2%), hypertension (1.4% *vs.* 15.5%), fatigue (4.9% *vs.* 8.6%), and proteinuria (0.0% *vs.* 3.0%) for paclitaxel alone and

bevacizumab plus paclitaxel, respectively. Among treated patients, 160 patients (46.2%) treated with paclitaxel alone and 243 patients (67.1%) treated with paclitaxel + bevacizumab reported at least one Grade 3–5 non–hematologic or Grade 4 or 5 hematologic adverse events. Among treated patients, 166 (48.0 %) treated with paclitaxel alone and 165 (45.6 %) treated with paclitaxel + bevacizumab died during the study or during follow–up.

Overall Discussion and Benefit –Risk assessment

PFS was the primary endpoint in the pivotal trial, with OS a secondary endpoint. As stated in the "EMEA Guideline for the Evaluation of Anticancer Medicinal Products in Man" both OS and PFS are acceptable primary endpoints. There should, however, be sufficient evidence available demonstrating that the chosen primary endpoint can provide a valid and reliable measure of clinical benefit in the patient population described by the inclusion criteria. If major differences in toxicity are expected in favour of the control regimen, OS should normally be selected as the most appropriate primary endpoint.

In order to exclude any possibility of bias, an independent review of the results is currently ongoing and will be submitted to the CHMP. Detailed information about the independent review of the radiologic images was provided by the MAH. The images will be reviewed by two independent radiologists who are blinded to the treatment arm, and in case of discordance a third radiologist will review the results and resolve the matter. Subsequently, an independent oncologist who is also blinded to the treatment arm will review the radiological assessment and complete the assessment on the basis of clinical information. This procedure would seem to satisfy the requirements for an independent review of outcome data. The difference in PFS is substantial in this patient population and it seems unlikely that the independent review will change the overall significance level although the absolute magnitude of prolongation in PFS cannot be assessed reliably from the data presented.

Sensitivity analyses, conducted by the MAH with the aim of assessing the impact of a potential investigator bias, provide reassurance that the substantial prolongation in PFS in the bevacizumab arm is unlikely to be attributable to bias. The CHMP agreed that the results of this independent review from E2100 study should be provided as a post approval commitment. The MAH will include a description of the independent review results in the prescribing information. Moreover the MAH will provide to the CHMP the results of the mature overall survival analysis from E2100 by 4Q 2007 and will update the summary of product characteristics accordingly.

The updated QoL analyses carried out show a trend towards a better QoL with bevacizumab treatment even using the most conservative imputation method. However, the fact that QoL data were obtained in an open-label phase III trial (i.e. in an unblinded manner) makes any assessment less reliable.

In the Phase III study AVF2119g, efficacy and safety of bevacizumab when combined with capecitabine was compared with capecitabine alone in patients previously treated with both an anthracycline and a taxane, either in the adjuvant or metastatic setting. In this study no significant prolongation of PFS was observed. Although this study cannot be directly relevant to the present application these contradicting results with respect to PFS were of concern to the CHMP. In order to further explore the efficacy and safety of bevacizumab and capecitabine combination, the MAH committed to provide the results of the ongoing clinical trial AVF3964g, studying the addition of bevacizumab onto standard chemotherapy in first-line metastatic breast cancer treatment. The results of AVF3694g are expected to become available in 2Q 2008.

The presented safety profile of the combination of paclitaxel and bevacizumab does not add any new or unexpected toxicities. It can be concluded that the benefit-risk ratio of Avastin in combination with paclitaxel in the treatment of metastatic breast cancer is positive.

3. CONCLUSION

- On 22 February 2007 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.

Follow-up measures undertaken by the Marketing Authorisation Holder
As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments:

Area[1]	Description	Due date[2]
Clinical	To provide to the CHMP the results of the independent review from E2100 study by 4Q 2007, and to include a description of the independent review results in the prescribing information.	4Q 2007
Clinical	To provide to the CHMP the results of the mature overall survival analysis from E2100 by 4Q 2007, and to update the prescribing information accordingly.	4Q 2007
Clinical	In light of the study results from trial AVF2119g, the MAH commits to further explore the efficacy and safety of bevacizumab and capecitabine combination within the ongoing clinical trial AVF3964g, studying the addition of bevacizumab onto standard chemotherapy in first-line metastatic breast cancer treatment.	2Q 2008
Clinical	To provide the results from an ongoing study BO17708, testing two dose levels of bevacizumab in combination with docetaxel as first-line treatment of metastatic breast cancer (2.5mg/kg/weekly equivalent and 5mg/kg/weekly equivalent) and to revisit the current dose recommendation for bevacizumab in metastatic breast cancer (5mg/kg/weekly equivalent) on the basis of the results from BO17708 trial.	2Q 2008

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance
2. Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.