London, 22 March 2007
Product name: **Herceptin**
EMEA/H/C/000278/II/0033

SCIENTIFIC DISCUSSION

Extension of the indication for use in combination with an aromatase inhibitor for the treatment of patients with HER2-positive and hormone receptor positive metastatic breast cancer, not previously treated with trastuzumab.

1. Introduction

Herceptin (trastuzumab) is currently approved for the treatment of Her2 over-expressing metastatic breast cancer, either as monotherapy if therapy with anthracycline and taxanes has failed or is contraindicated, or in combination with paclitaxel in patients who have not received prior chemotherapy for metastatic disease and for whom an anthracycline is not suitable or in combination with docetaxel in patients who have not received prior chemotherapy for metastatic disease.

Trastuzumab was recently approved for the adjuvant treatment of early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).

The MAH has submitted data from the BO16216 trial (TAnDEM study) to support an extension of the indication to include treatment of patients with Her2 positive, hormone receptor positive breast cancer in combination with an aromatase inhibitor.

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2. Clinical aspects

Clinical pharmacology

In study BO16216, patients were given a weekly Herceptin dose schedule (a loading dose of 4 mg/kg on day 1 followed by a weekly dose of 2 mg/kg). This is the dose schedule of Herceptin approved for metastatic breast cancer. Anastrozole was given at a daily dose of 1.0 mg.

Pharmacokinetic analysis was planned for at least 16 patients per arm. However, on completion of the study, data were available for the analysis of Herceptin in only 6 evaluable patients. Similarly, data for the analyses of anastrozole were only available for 7 evaluable patients (one in the anastrozole alone group and 6 in the anastrozole plus Herceptin group). Consequently, the data are of a descriptive nature, but suggest that the pharmacokinetic profile of Herceptin when given together with anastrozole compares well with historical values for Herceptin at the same dose in other studies and the pharmacokinetic profile of anastrozole was generally as expected. Within the limitations of the data set, achieved concentrations of anastrozole were similar with or without coadministration of Herceptin.

For pharmacodynamic analysis, serum estrone and estradiol levels were measured at baseline and at week 12. Serum shed extracellular domain of HER2 receptor (ECD) was assessed at baseline, week 12, and bi-monthly after week 12 until the end of study. In the presence of Herceptin, anastrozole reduces concentrations of estrone and estradiol effectively. Baseline serum shed ECD did not seem to correlate with best tumor response. Although the median baseline ECD values seemed higher in patients experiencing progressive disease compared with patients with stable disease or partial response, no conclusions could be reached because of the variability of baseline ECD levels.

2.2. Clinical efficacy

The MAH has conducted a single pivotal trial to investigate the effect of trastuzumab in combination with anastrozole. Study BO16216 (TAnDEM) is an open-label randomised, multi-centre study in postmenopausal women with metastatic breast cancer.

The study consisted of two treatment phases, main and extension. For patients in the anastrozole-plus-Herceptin arm, the main phase was defined as the first 24 months of treatment or until PD, and the extension phase was defined as the treatment period after 24 months and a withdrawal from the study was either in the main phase or the extension phase. For patients in the anastrozole-alone arm, the main phase was defined as the first 24 months of treatment or until PD (where they crossed over to Herceptin) and the extension phase was defined as the treatment period after PD (if earlier than 24 months) or after 24 months. A patient in the anastrozole-alone arm could withdraw from the main

phase of the study at PD, but continue in the study extension phase receiving a Herceptin containing regimen and subsequently withdraw from the extension phase and the study.

Patients with a histological or cytological diagnosis of metastatic breast cancer and measurable or evaluable disease who are suitable for endocrine therapy with anastrozole, postmenopausal, previously determined to be ER+ve and/or PgR+ve and HER2 overexpression, who have acceptable LVEF and haematological status, acceptable liver and renal function and performance status (ECOG scale 0 or 1) would be eligible for the study.
Anastrozole was administered at a dose of 1 mg/day which is the recommended dose. Trastuzumab was administered at a 4 mg/kg loading dose iv over 90 min, followed by weekly doses of 2 mg/kg iv over 30 min.

Primary objective was to evaluate the efficacy of the combination of trastuzumab and anastrozole as compared with anastrozole alone in patients with HER2 overexpression and hormone-sensitive metastatic breast cancer.

Secondary objectives were: to characterize the safety profile of the combination of Herceptin and anastrozole as compared to anastrozole alone, to determine and compare the overall clinical benefit rate (CBR) between the two treatment arms (defined as stable disease for ≥ 6 months, complete response, or partial response) to determine and compare the overall survival, duration of response, and 2-year survival in the two treatment arms.

Primary endpoint

Efficacy was determined by progression-free survival (PFS). Progression is defined according to the WHO criteria (Handbook for Reporting Results of Cancer Treatment)

Secondary endpoints were:

- *Clinical Benefit Rate (CBR):* Unlike assessment of response rate, patients who do not have bidimensionally measurable disease at baseline were included in the assessment of CBR.
- *Duration of Response and Time to Response*.
- *Overall Survival:*
- *Two-Year Survival* defined as the Kaplan Meier estimate at 2 years (730 days).
- *Tumour Response Rates (Best response and overall response):*
- *Time to progression (TTP):*.
- *Performance Status (ECOG):*

Interim analysis

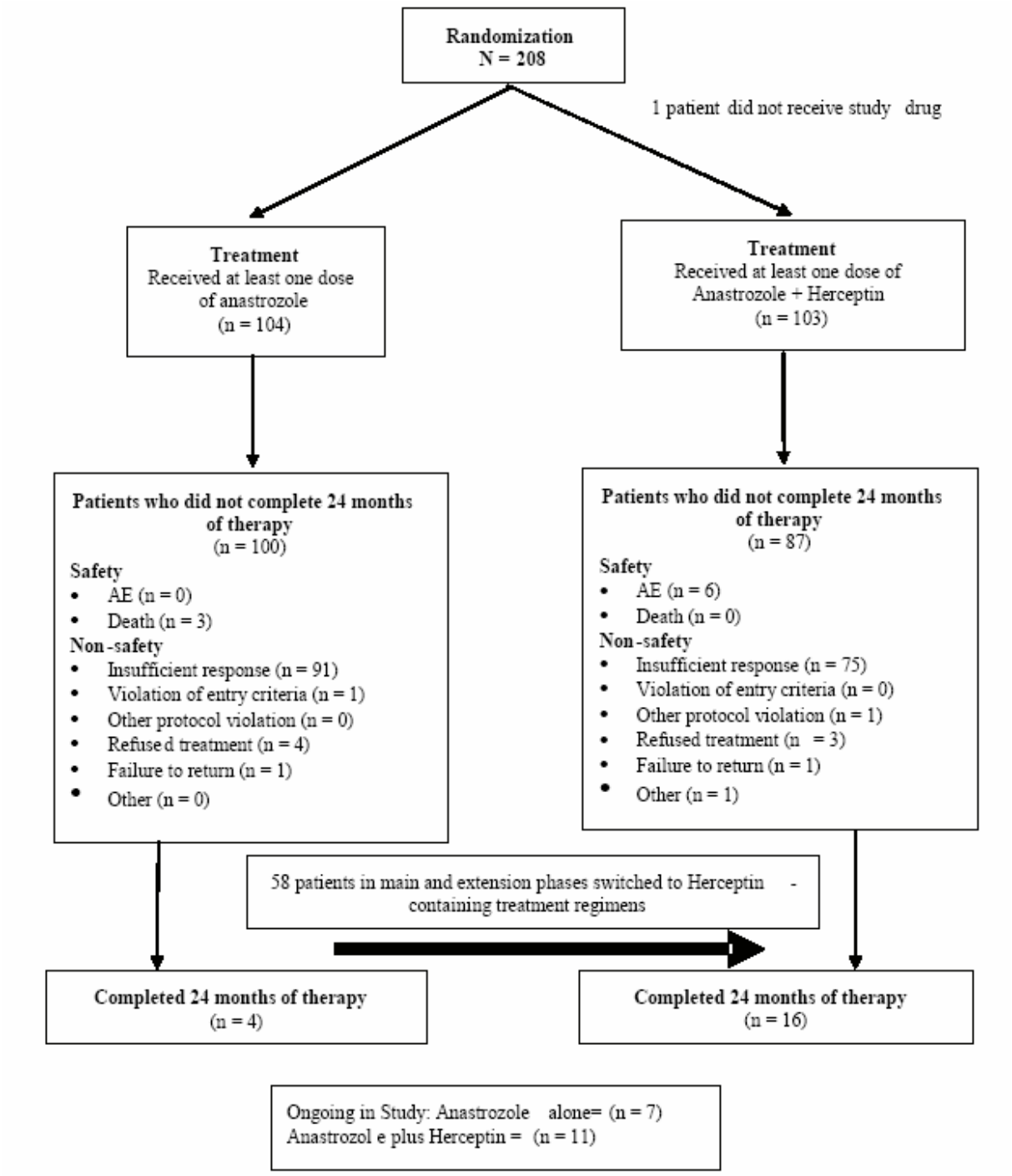
An interim analysis was to be performed when approximately 60 events (based on investigator assessments), were observed in the study. The interim analysis was to be performed by a Roche statistician not directly involved in the study and was based on the primary parameter, progression-free survival (PFS). The secondary parameter, survival, was also analyzed. The difference in PFS and survival between the treatments was tested with a log rank test.

Sample size

Anticipating a median PFS of 7 months in the group of patients treated with anastrozole alone and a prolongation of the PFS by 4 months (57% increase) when adding Herceptin, a log rank test on progression-free survival (PFS) requires 101 patients per arm, recruited over 24 months and followed up for at least 24 months, to achieve 80% power at a 2-sided significance level of 5% (≤ 0.0493), assuming that 187 events are seen. This calculation accounts for a drop out rate of 10%.

Randomisation

A minimization procedure according to Pocock and Simon balancing for the existence of liver metastase, tumor assessment, relapse following adjuvant tamoxifin and bisphosphonate therapy at time of enrolment was used for treatment allocation. An automated Interactive Voice Response System (IVRS) was applied for treatment allocation.



Out of 208 randomized patients, 1 patient did not receive study drug and was excluded from the FAS and safety population. The remaining 207 patients, who received either Arimidex-alone (n = 104) or Arimidex + Herceptin (n = 103), were included in the FAS and safety population.

The per protocol set (PPS) consisted of 193 patients (95 and 98 patients in the Arimidex-alone and Arimidex-plus-Herceptin arm, respectively), and included all patients who did not have a major violation of the protocol.

In the anastrozole-alone arm, 9 patients were excluded from the PPS for the following reasons: prior chemotherapy; HER2 overexpression/amplification not documented; no protocol-specified tumor (no metastatic disease); or anastrozole compliance. In the anastrozole-plus- Herceptin treatment arm, 6 patients were excluded from the PPS because of the following reasons: prior chemotherapy; HER2 overexpression/amplification not documented; anastrozole compliance; or no study medication given.

Demographic data

The following table shows demographic data at baseline

	ARIMIDEX ALONE N = 104	ARIMIDEX PLUS HERCEPTIN N = 103
Sex		
MALE	-	-
FEMALE	104 (100%)	103 (100%)
n	104	103
Race		
CAUCASIAN	73 (70%)	82 (80%)
BLACK	1 (<1%)	1 (<1%)
ORIENTAL	7 (7%)	6 (6%)
OTHER	23 (22%)	14 (14%)
n	104	103
Age in years		
Mean	55.5	57.4
SD	10.75	10.65
Median	54.0	56.0
n	104	103
Weight in kg		
Mean	65.86	68.82
SD	13.580	15.270
Median	67.00	67.00
n	102	103
Height in cm		
Mean	159.472	159.141
SD	6.7516	6.9939
Median	160.000	159.000
n	101	103

Efficacy Results

The primary endpoint in this study was progression free survival. All 207 patients were assessed by an investigator and subsequently by a Response Evaluation Committee (REC) as long as they progressed during the first 24 months of treatment in the main phase of the study. If a PD occurred during the extension phase, no REC assessment was carried out.

28 patients were not evaluated by the REC because they withdrew from the study prior to getting a radiological exam, or the selected baseline tumours could not be followed up in later radiological exams. In situations where the investigator assessment was different from the REC assessment, an independent oncologist made the definitive assessment- this process was called reconciliation.

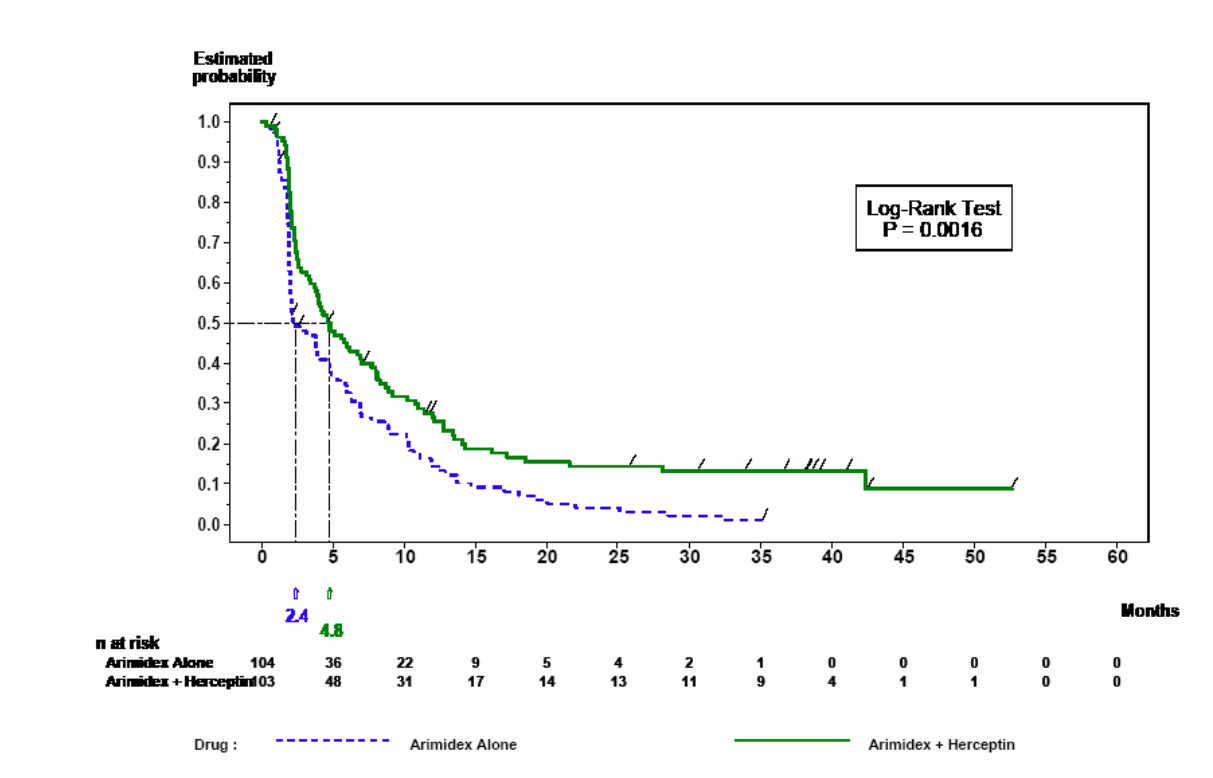
The following table shows the data for progression free survival as assessed by the different assessment procedures.

	Arimidex Alone (N = 104)	Arimidex plus Herceptin (N = 103)
Progression-free Survival Time (months)		
Reconciled Assessment		
N	104	103
Median (1)	2.4	4.8
95% CI for Median (1)	2 - 4.6	3.7 – 7
P-Value (Log-rank Test)	0.0016	
Stratified analysis with all stratification factors (Cox regression, reconciles assessment)		
P-Value (Log-rank Test)	0.0132	

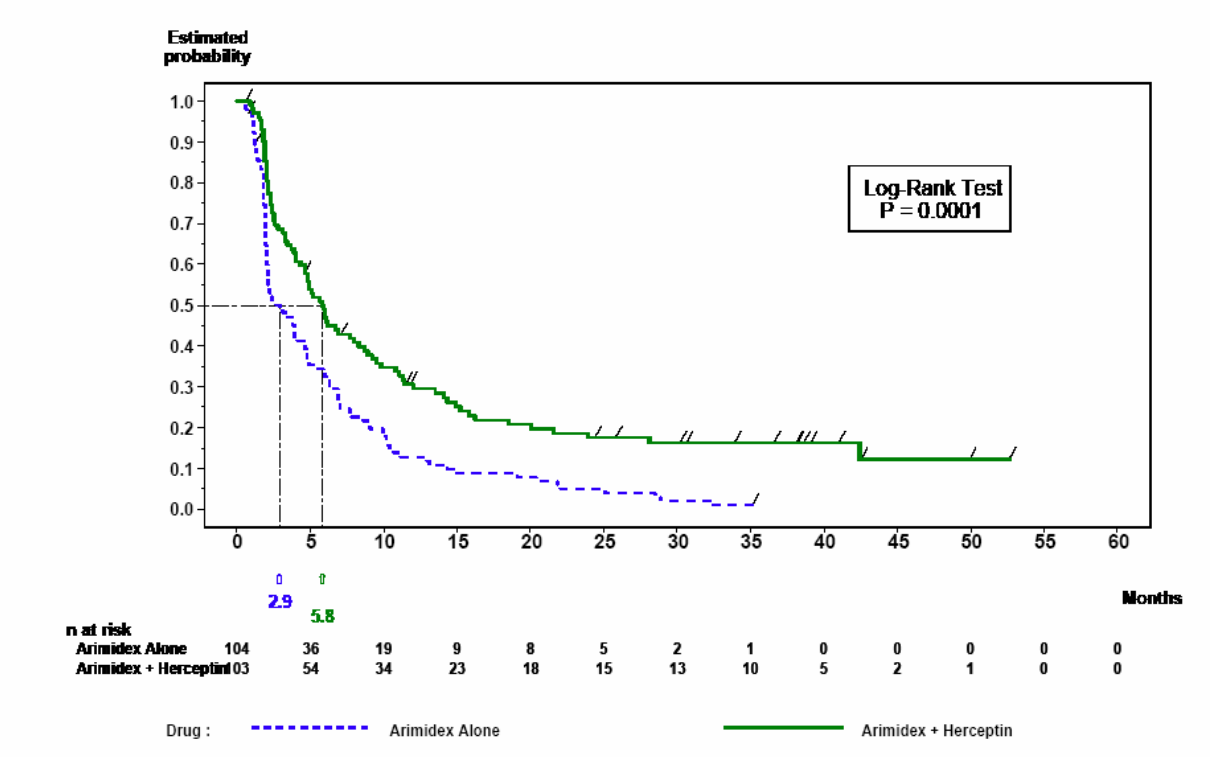
Investigator Assessment		
N	104	103
Median (1)	2.9	5.8
95% CI for Median (1)	2.1 - 4.5	4.6 - 8.3
P-Value (Log-rank Test)	0.0001	
Response evaluation committee		
N	87	92
Median (1)	3.9	8.1
95% CI for Median (1)	2.1 – 6	4.4 - 12.1
P-Value (Log-rank Test)	0.0361	

Kaplan Meier estimates

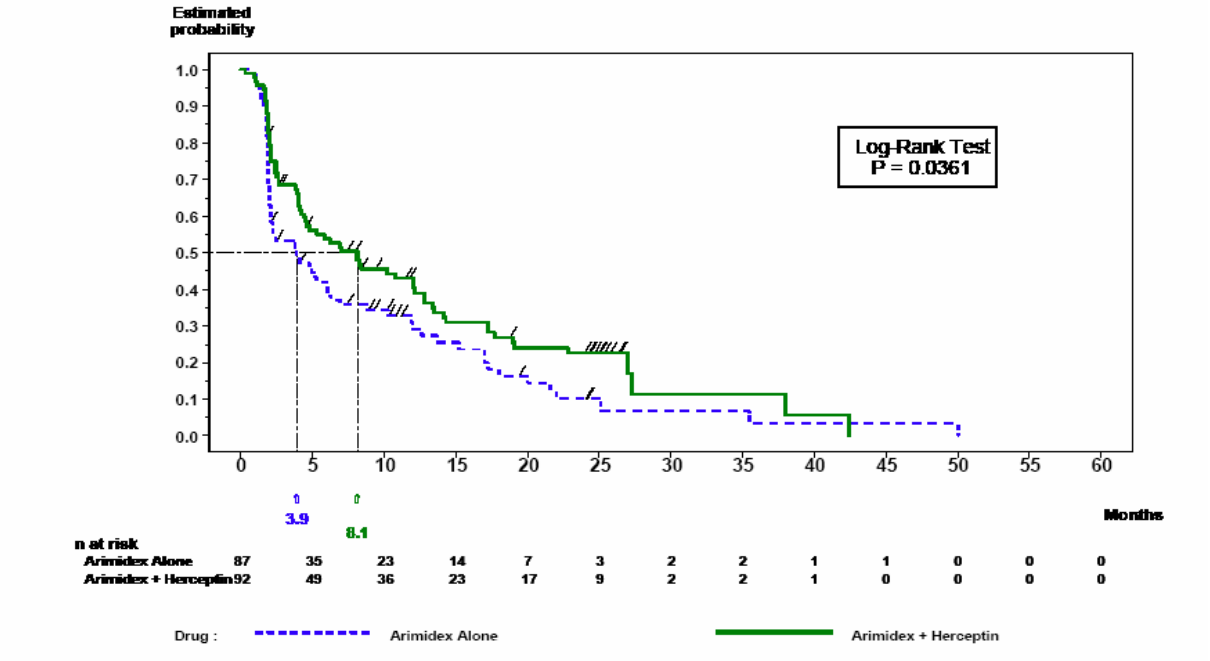
Kaplan Meier Curve of progression free survival (reconciled assessment)



Kaplan Meier Curve of progression free survival (investigator assessment)



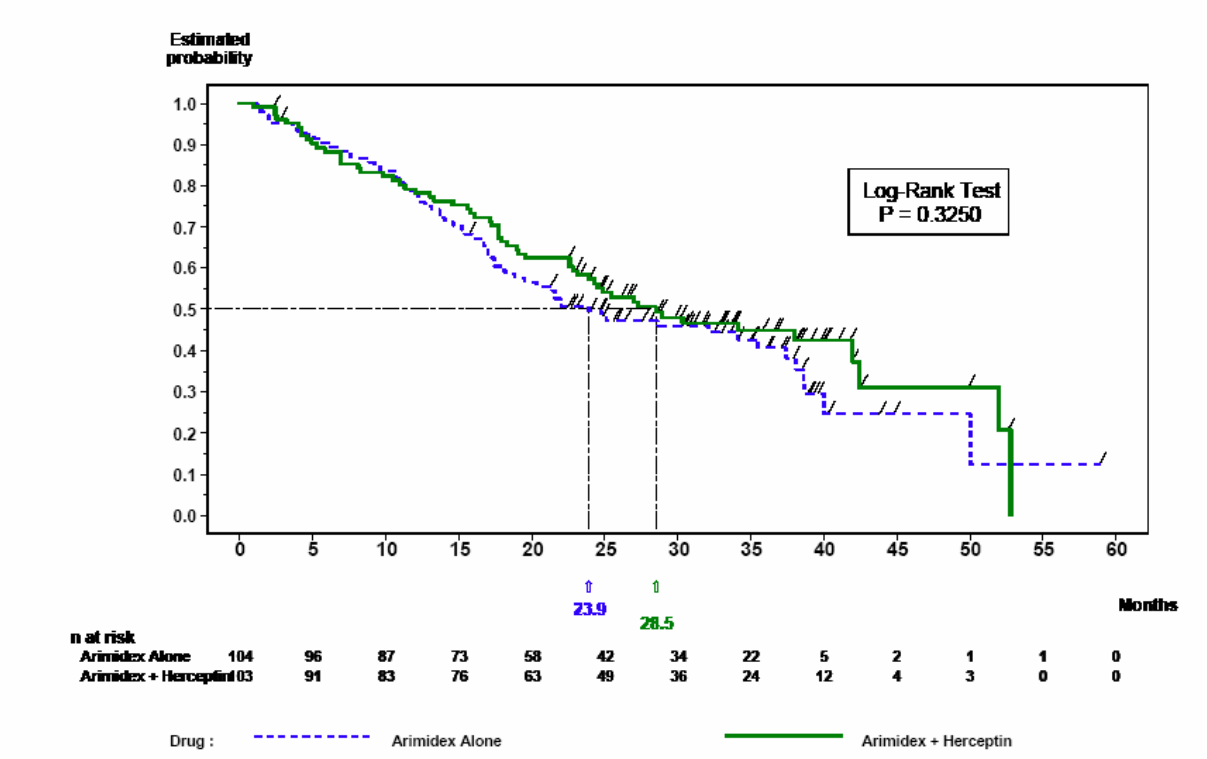
Kaplan Meier Curve of progression free survival (response evaluation committee assessment)



Secondary efficacy parameters

The following table and Kaplan Meier curve shows overall survival in the FAS population

	Arimidex Alone (N = 104)	Arimidex plus Herceptin (N = 103)
Number Dying	64 (61.5 %)	58 (56.3 %)
Number Surviving (censored)	40 (38.5 %)	45 (43.7 %)
Survival Time (months)		
Median (1)	23.9	28.5
95% CI for Median (1)	18.2 - 37.4	22.8 - 42.4
P-Value (Log-rank Test)		0.325



The following table shows the overall tumor response rate for the reconciled assessment

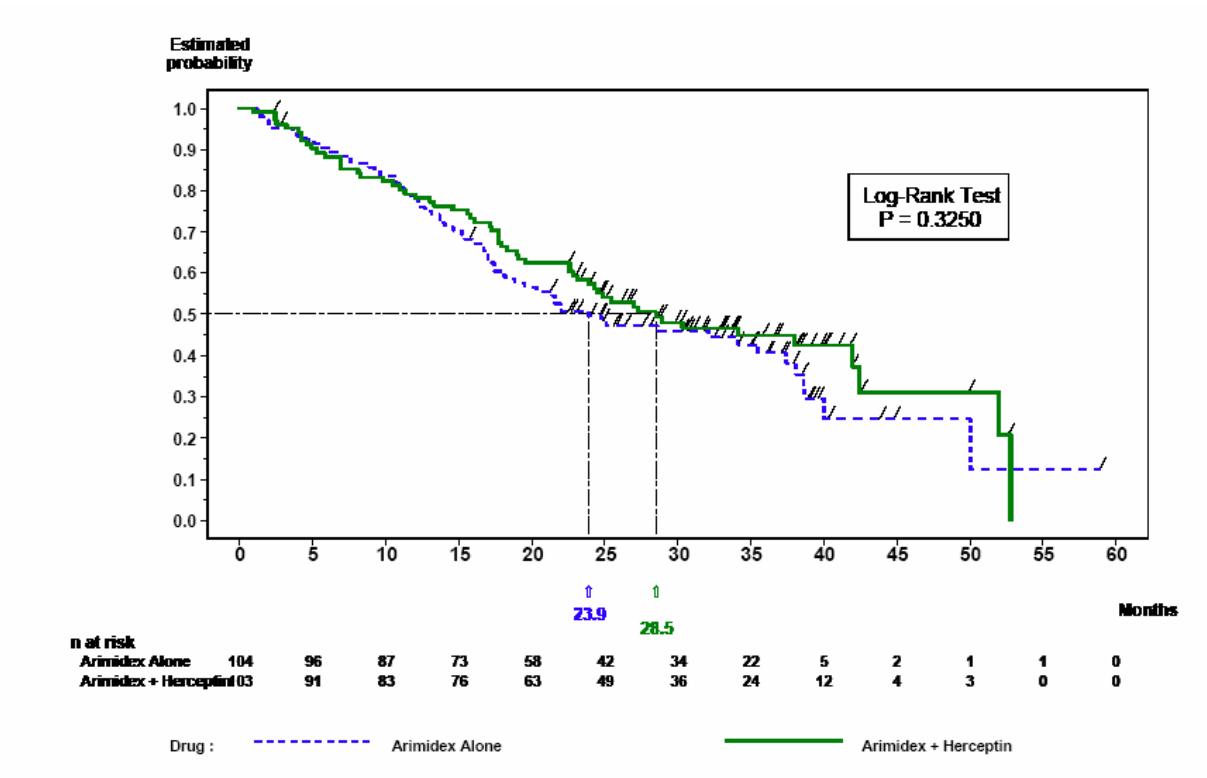
	Arimidex Alone (N = 73)	Arimidex plus Herceptin (N = 74)
Responders	5 (6.8 %)	15 (20.3 %)
Non-responders	68 (93.2 %)	59 (79.7 %)
Exact 95% CI for Overall Response Rate (1)	(2.26, 15.27)	(11.81, 31.22)
Difference in Overall Response Rates		13.4
95% CI for the difference in Overall Response Rates (2)		(1.82, 25.02)
P-Value (Chi-squared Test)		0.018

The following table shows the clinical benefit rate for the reconciled assessment

	Arimidex Alone (N = 104)	Arimidex plus Herceptin (N = 103)
Clinical Benefit		
Yes	29 (27.9 %)	44 (42.7 %)
No	75 (72.1 %)	59 (57.3 %)
Exact 95% CI for Response Rates (1)	(19.54, 37.53)	(33.02, 52.85)
Difference in Clinical Benefit Rates		14.8
95% CI for the difference in Clinical Benefit Rates (2)		(1.42, 28.25)
P-Value (Chi-squared Test)		0.~~018~~026

Secondary efficacy parameters

The following Kaplan Meier curve shows overall survival in the FAS population



Analysis of subpopulations

A Cox regression analysis was performed on the reconciled progression free survival. The stratification factors and the following baseline characteristics were included in the model: Relapse following adjuvant Tamoxifen, Bisphosphonate therapy, Age classes , Prior hormonal therapy , Regions , Race , Number of metastatic sites, Sites of metastases (liver metastases, lung metastases, bone metastases, soft tissues metastases), Histology (moderately, poorly differentiated), locally tested ER/PgR status for primary tumor.

Hazard ratios that were obtained for these subgroups did not show inconsistencies and showed a homogenous effect. For two subgroups, patients with prior hormonal therapy (9 patients), and patients with ER negative/PgR positive primary cancer (15 patients), the confidence interval was very wide suggesting that no conclusions can be made for these two subgroups.

	N	Hazard Ratio	Confidence Interval
Overall	207	0.627	0.469 – 0.839
Tumor assessment			
measurable disease	161	0.716	0.516 – 0.994
non-measurable disease	46	0.458	0.243 – 0.863
Relapse following adjuvant Tamoxifen			
< 12 months	100	0.605	0.398 – 0.920
≥ 12 months	23	0.922	0.367 – 2.315
no adj Tamoxifen	84	0.577	0.362 – 0.920
Bisphophonate therapy			
Yes	50	0.896	0.504 – 1.594
No	157	0.561	0.399 – 0.789
Age classes			
< 56 yr	104	0.630	0.415 – 0.956
≥ 56 yr	103	0.625	0.415 – 0.941
Prior hormonal therapy (other than tamoxifen)			
Yes	9	1.646	0.325 – 8.341
No	197	0.625	0.464 – 0.841
Regions			
America	35	1.227	0.601 – 2.504
Asia	47	0.625	0.330 – 1.183
Europe-East	50	0.838	0.467 – 1.504
Europe-West	54	0.412	0.225 – 0.755
AUS, Israel, South Africa	21	0.378	0.129 – 1.105
Race			
Caucasian	155	0.642	0.458 – 0.899
non- Caucasian	52	0.710	0.392 – 1.287
Number of metastatic sites			
1	50	0.616	0.314 – 1.210
2	71	0.439	0.265 – 0.729
3	47	0.577	0.313 – 1.064
≥ 4	39	0.682	0.338 - 1.375
Liver metastases at baseline			
yes	62	0.839	0.499 – 1.412
no	145	0.543	0.380 – 0.774
Lung metastases at baseline			
yes	91	0.758	0.494 – 1.163
no	116	0.550	0.369 – 0.820
Bone metastases at baseline			
yes	117	0.674	0.463 – 0.983
no	90	0.536	0.333 – 0.864
Soft tissue metastases at baseline			
yes	90	0.535	0.347 – 0.824
no	117	0.705	0.476 – 1.044
Histology			
moderately	68	0.653	0.393 – 1.086
poorly	70	0.920	0.565 – 1.500
ER/PgR status for primary tumor			
ER positive/PgR positive	114	0.646	0.483 – 0.951
ER positive/PgR negative	53	0.545	0.301 – 0.984
ER negative/PgR positive	15	3.065	0.642 – 14.630

Overall discussion of efficacy

The MAH has submitted the results from a single pivotal trial of anastrozole alone or in combination with trastuzumab. The study was randomised and open label. The doses chosen for combination therapy were identical to the recommended doses in monotherapy, no dedicated dose finding or interaction study has been performed. From the mechanisms of action of both drugs this is considered acceptable.

Primary endpoint was progression free survival and secondary endpoints were overall survival, tumor response rate, clinical benefit rate (stable disease for ≥ six months or complete response or partial response) time to progression, duration of response, time to response, and 2-year survival. The chosen endpoint are considered relevant and in conformance with the anti-cancer medicinal product guideline (CPMP/EWP/205/95/Rev.3/Corr, Dec 2005). QoL measures were not included which would not be useful in an open label trial. Methods and procedure for assessing disease progression are acceptable in general. Several amendments were introduced during the conduct of the trial. The most important of these was amendment E that allowed the cross-over of patients that had disease progression in the anastrozole only group.

The primary endpoint progression free survival was met in all three assessment procedures which became necessary because unblinded investigator assessment of progressive disease was checked by an independent blinded assessment. Median progression free survival was 2.4 months with anastrozole monotherapy and 4.8 months with the combination of anastrozole and trastuzumab. There was no benefit with respect to overall survival but the other secondary endpoints tumor response rate, clinical benefit rate (stable disease for ≥ six months or complete response or partial response) time to progression were concordant to the primary endpoint. No effect was seen for duration of response, time to response. Although the secondary endpoint overall survival was not met the results are considered as relevant and clinically meaningful. Due to the high crossover rate to the trastuzumab plus anastrozole group after disease progression an effect of trastuzumab on overall survival is likely to be diluted. This was corroborated by a post-hoc analysis suggesting that patients in the combination of Herceptin plus anastrozole either upfront (28.5 months) or after cross-over (25.1 months) had a larger benefit in terms of survival than patients treated with anastrozole alone (17.2 months).

Subgroup analyses were consistent and did not give an indication for lack of efficacy in clinically relevant subgroups. Analysis of the PFS results for patients that were enrolled after the amendment was provided and it was in line with the independent review results, which rules out significant bias.

2.3 Clinical safety

The present application is based on results of trastuzumab combined with anastrozole in the treatment of patients with HER2 overexpression and estrogen receptor (ER) or progesterone receptor (PgR) positive metastatic breast cancer. These results were obtained from one randomized, parallel-group, open-label, phase III trial (BO16216) sponsored by Roche and Genentech, in which 207 patients (208 randomized) received either the combination therapy of trastuzumab and anastrozole or anastrozole monotherapy.

Patient Disposition

A total of 208 patients were randomized and 207 patients were treated at 77 centres in 22 countries. Of the 207 patients, 104 were randomized to the anastrozole-alone arm and 103 were randomized to the anastrozole-plus trastuzumab arm.

All 207 patients treated in the study were included in the safety analysis population. Demography, baseline characteristics, and safety data were evaluated using the safety population.

Of the 104 patients from the anastrozole-alone arm, 58 started a Herceptin containing regimen after PD was assessed by the investigator (either during the main phase or extension phase of the study) and entered or continued in the extension phase. Two of the 58 patients who crossed over, had minimal information available on exposure and were excluded from the exposure table, but are included in the safety results. An additional 15 patients started Herceptin after they left the study (information was recorded during the survival follow-up phase) and their data are not captured in the after crossover safety outputs. This high proportion of crossover patients can be regarded as a confounding factor for

the survival analysis, making the contribution of Herceptin to overall survival in the anastrozole-alone arm unclear.

A total of 187 patients were withdrawn from the study during the main phase, 100 patients in the anastrozole-alone arm and 87 in the anastrozole plus Herceptin arm.

The majority of patients (166 out of 207) withdrew from the study due to insufficient therapeutic response, which was progression of disease (91 patients from the anastrozole-alone arm and 75 patients from the anastrozole plus trastuzumab arm). One patient (29152/4608) in the anastrozole-alone arm was withdrawn from the study due to a violation of selection criteria at entry (pre-menopausal). One patient in the anastrozole plus trastuzumab arm (33339/8301) was withdrawn from the study because she received radiation to the only target lesion, which was a protocol violation.

In the main phase, very few patients (9) were withdrawn from the study due to safety reasons (3 patients in the anastrozole-alone arm, and 6 in anastrozole plus trastuzumab arm). The 3 withdrawals from the study in the anastrozole-alone arm were due to deaths, and for 2 patients (33339/8304, and 33327/8322), the cause of death was progression of disease, and for the other patient (33339/8302) the cause of death was adverse events of respiratory tract infection and myocardial infarction. No withdrawals due to death were recorded in the anastrozole plus trastuzumab arm.

Six patients in the anastrozole plus trastuzumab arm withdrew due to AEs [cardiac failure (2x), cardiotoxicity (2x), endometrial cancer (1x) and cervix carcinoma (1x)]. Two of the cardiac adverse events were asymptomatic drops in left ventricular ejection fraction (LVEF).

For patients in the anastrozole-alone treatment arm who experienced disease progression and crossed over to trastuzumab treatment, data obtained after the start of trastuzumab treatment are not included in these comparative analyses, but are presented separately.

Median trastuzumab treatment duration in the anastrozole-plus-trastuzumab treatment arm was 26 weeks in the safety population (n = 103), with a median of 25 trastuzumab infusions. The median cumulative trastuzumab dose was 3990 mg.

The median treatment duration of anastrozole in the anastrozole-alone arm was 98 days compared with 189 days in the anastrozole-plus-trastuzumab treatment arm. Cumulative median anastrozole dose was 97 mg for patients taking anastrozole-alone compared to 180 mg for patients taking anastrozole-plus-trastuzumab. Patients in the anastrozole-plus-trastuzumab arm had almost double the exposure to anastrozole, and almost double the cumulative dose of anastrozole. The longer treatment duration in the anastrozole-plus-trastuzumab arm is due to longer time-to-disease progression.

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Adverse events

An overview of the incidence of all adverse events in both treatment arms before cross over is given. For deaths, all events until database lock (May 12th 2006), regardless of phase of study or crossover is provided.

Overview of Adverse Events (Safety Population-Before Crossover)

	anastrozole-alone Arm n = 104	anastrozole plus Herceptin Arm n = 103
	No of Patients with AE (%)	No of Patients with AE (%)
At least one AE	68 (65%)	90 (87)
AEs related to trial treatment	16 (15%)	55 (53%)
Grade III AE	16 (15%)	24 (23%)
Grade IV AE	1 (1%)	5 (5%)
Serious AE	6 (6%)	24 (23%)
Serious AE related to trial treatment	0 (0%)	4 (4%)
AEs leading to discontinuing trial treatment	1 (1%)	9 (9%)
Deaths due to PD*	59 (57%)	56 (53%)
Deaths not due to PD*	5 (5%)	2 (2%)

*Includes all deaths until database lock independent of the study phase (main phase, extension phase or FU for survival) or crossover. One patient died after cross-over to Herceptin.

Overall, 65% (68/104) of patients in the anastrozole-alone arm and 87% (90/103) of patients in the anastrozole-plus-trastuzumab arm reported at least one adverse event during the study. As expected, there was a higher incidence of common, non-serious adverse events in patients treated with anastrozole-plus-trastuzumab (total number of AEs reported: 636 for anastrozole-plus-trastuzumab versus 246 for anastrozole-alone), reflecting the addition of trastuzumab side effects to those of anastrozole and likely also reporting bias due to longer treatment and thus longer AE reporting period. Additionally, patients in the combination arm had more contacts with study staff as they had to get trastuzumab infusions every week. In comparison, patients treated with oral anastrozole alone returned to sites only for scheduled visits (every 4 weeks up to 3 months and every 8 weeks thereafter).

Considerably more patients had drug-related adverse events in the combination arm compared to anastrozole-alone arm. This can be explained by the additive adverse effect of two anticancer drugs and probably also by reporting bias.

There was an overall higher incidence of patients with grade 3 and 4 adverse events in the anastrozole-plus-trastuzumab: Grade 3 AEs were experienced by 15.4% and 23.3% of patients in the anastrozole-alone arm and anastrozole-plus-trastuzumab arm, respectively. Grade 4 AEs were reported by 1 patient in the anastrozole-alone arm and 5 patients in the anastrozole-plus-trastuzumab arm.

Fatigue, vomiting, and diarrhoea were the three most frequent AEs in the anastrozole-plus-trastuzumab arm, followed by pyrexia, nausea, and nasopharyngitis. For the anastrozole-alone treatment arm, fatigue, arthralgia, and dyspnoea were the three most common AEs. These most common adverse events have been typically associated with trastuzumab and/or anastrozole administration.

Common Adverse Events >10% in Either Treatment Arm (Before Crossover)

ael3pco Summary of Adverse Events With an Incidence Rate of at Least 10 % by Trial Treatment
Protocol(s): I16216F
Analysis: SAFETY Center: ALL CENTERS

Adverse Event	ARIMIDEX ALONE N = 104 No. (%)	ARIMIDEX PLUS HERCEPTIN N = 103 No. (%)
FATIGUE	10 (10)	22 (21)
DIARRHOEA	8 (8)	21 (20)
VOMITING	5 (5)	22 (21)
ARTHRALGIA	10 (10)	16 (15)
PYREXIA	7 (7)	18 (17)
BACK PAIN	7 (7)	16 (15)
DYSPNOEA	9 (9)	13 (13)
NAUSEA	5 (5)	17 (17)
COUGH	6 (6)	14 (14)
HEADACHE	6 (6)	14 (14)
NASOPHARYNGITIS	2 (2)	17 (17)
BONE PAIN	6 (6)	11 (11)
CONSTIPATION	5 (5)	12 (12)
CHILLS	-	16 (15)

Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Note: For patients from the Arimidex Alone arm who switched to Herceptin, only AEs before the 1st Herceptin administration are displayed
AE13 23JUN2006:18:29:05

Gastrointestinal disorders were the most frequently reported adverse events, being reported by 23% of anastrozole-alone arm patients and 52% anastrozole-plus-trastuzumab arm patients. The most frequently reported adverse events within this SOC were diarrhoea (8% vs 20%) and vomiting (5% vs 21%) in the anastrozole-alone and anastrozole-plus-trastuzumab arms, respectively.

Cardiac disorders were seen more frequently in the anastrozole-plus-trastuzumab arm (13%) compared to the anastrozole-alone arm (2%); however, some of the cardiac AEs reported were asymptomatic (ie, LVEF decreases), but were reported as AEs since they lead to withdrawal of the patient from the study.

In the anastrozole-alone arm, a majority of the adverse events were considered mild (grade 1 and 2) in intensity (90 patients reported 217 grade 1 and 2 events). Sixteen patients reported 27 adverse events of severe (grade III) intensity, and 1 patients reported 2 adverse events considered life-threatening (grade IV) in intensity in the anastrozole-alone arm (respiratory tract infection and myocardial infarction).

In the anastrozole-plus-trastuzumab study arm, a majority of the adverse events were considered mild (grade 1) in intensity (146 patients reported 584 grade 1 and 2 events). Twenty-four patients reported 47 grade III adverse events, and 5 patients reported 5 grade IV adverse events. The grade IV events reported were lower respiratory tract infection, dyspnoea, 2 events of hypercalcaemia, and myocardial ischemia.

Grade 3 and 4 cardiac adverse events were comparable between the two treatment arms (one grade 3 and one grade 4 event per treatment arm)

A total of 55 patients (54%) reported 126 adverse events which the investigator considered to be related to anastrozole-plus-trastuzumab treatment. Most related adverse events were infusion related events reported in the administrative site condition with chills (13 related events), pyrexia (9 related events), and fatigue (7 related events) being the highest reported events. Greater than or equal to 6 percent of related adverse event reported were diarrhea, rash, and headache. These related adverse events are also typically seen with trastuzumab administration.

Nine of the 13 cardiac disorders were considered related to study treatment. One event of serious cardiac disorder (event of cardiac failure) was considered related to study treatment.

The number of patients withdrawing from trial treatment due to an adverse event was low in both treatment arms but occurred more frequently in the anastrozole-plus-trastuzumab treatment arm (9 cases), than in the anastrozolealone arm (1 case).

Majority of the adverse events (5 out of 9) that lead to discontinuation of trial treatment in the anastrozole-plus-trastuzumab were cardiac abnormalities (2 with cardiac failure, 2 with cardiotoxicity, and one with myocardial infarction). All of these 5 cardiac adverse events were considered related to trial treatment by the investigator.

Serious adverse events and deaths

Serious adverse effects were also increased in the anastrozole-plus-trastuzumab treatment arm (23%) compared to the anastrozole-alone (6%) arm.

There were a total of 122 deaths (60% of FAS): 64 in the anastrozole-alone arm and 58 in the anastrozole-plus-trastuzumab arm. The majority of the deaths, (59 in anastrozole-alone and 56 in anastrozole plus trastuzumab) were due to progressive disease. There were 7 deaths not due to PD. Five deaths were reported in the anastrozole-alone arm. Two additional deaths were reported in the anastrozole-plus-trastuzumab treatment arm: 1 due to unknown cause, and 1 due to gastrointestinal hemorrhage.

Before crossover, there was 1 death due to 2 adverse events: a patient (33339/8302) with both myocardial infarction and respiratory tract infection (it was unclear which of these 2 events lead to death, thus both documented as leading to death). An additional patient died from an adverse event of sudden death (29168/3601) (not captured in the below Table) after crossover, according to the Case Report Form, the cause of death was probably cardiac failure; however, no autopsy was performed.

Less patients in the anastrozole-alone arm experienced a serious adverse event than in the anastrozole-plus-trastuzumab arm. Serious adverse events were reported for 6 patients (experiencing 9 SAEs) in the anastrozole-alone arm (6%) prior to crossover, and 24 patients (experiencing 47 SAEs) in the anastrozole-plus-trastuzumab arm (23%).

Gastrointestinal disorders SAEs were reported in 7 (7%) patients in the anastrozole-plus-trastuzumab arm compared with no anastrozole-alone arm patients. Infection and infestations were reported in 4 anastrozole-plus-trastuzumab patients, and 3 anastrozole-alone arm patients, and General Disorders and Administration Site Conditions were reported in 5 anastrozole plus trastuzumab arm patients and 1 patient in the anastrozole-alone arm.

The most common serious adverse event was vomiting reported in 3 patients in the anastrozole-plus-trastuzumab arm. All of the other SAEs were experienced by 1 or 2 patients each. Three SAEs were reported as cardiac disorders, 2 events of myocardial infarction (1 patient in each treatment arm), and an event of myocardial ischemia in a patient in the Anastrozole-plus-trastuzumab arm.

Incidence of Serious Adverse Events by Body System (Before Crossover)

aellspco Summary of Adverse Events by Body System and Trial Treatment
Serious Adverse Events
Protocol(s): I16216F
Analysis: SAFETY Center: ALL CENTERS

Body System/ Adverse Event	ARIMIDEX ALONE N = 104 No. (%)	ARIMIDEX PLUS HERCEPTIN N = 103 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	6 (6)	24 (23)
Total Number of AEs	9	47
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	-	7 (7)
VOMITING	-	3 (3)
NAUSEA	-	2 (2)
ABDOMINAL PAIN	-	1 (<1)
CONSTIPATION	-	1 (<1)
DIARRHOEA	-	1 (<1)
GASTRITIS	-	1 (<1)
INTESTINAL OBSTRUCTION	-	1 (<1)
SMALL INTESTINAL OBSTRUCTION	-	1 (<1)
Total Number of AEs	-	11
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	3 (3)	4 (4)
CATHETER RELATED INFECTION	1 (<1)	-
FOLLICULITIS	-	1 (<1)
LOWER RESPIRATORY TRACT INFECTION	-	1 (<1)
MALARIA	1 (<1)	-
RESPIRATORY TRACT INFECTION	1 (<1)	-
STREPTOCOCCAL SEPSIS	-	1 (<1)
URINARY TRACT INFECTION PSEUDOMONAL	-	1 (<1)
Total Number of AEs	3	4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	1 (<1)	5 (5)
CHEST PAIN	-	2 (2)
PAIN	-	2 (2)
PYREXIA	1 (<1)	1 (<1)
ASTHENIA	-	1 (<1)
Total Number of AEs	1	6
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total Pts With at Least one AE	-	6 (6)
CONTUSION	-	1 (<1)
FALL	-	1 (<1)
FEMUR FRACTURE	-	1 (<1)
HIP FRACTURE	-	1 (<1)
HUMERUS FRACTURE	-	1 (<1)
UPPER LIMB FRACTURE	-	1 (<1)
Total Number of AEs	-	6

Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Note: For patients from the Arimidex Alone arm who switched to Herceptin, only AEs before the 1st Herceptin administration are
displayed
AE11 23JUN2006:18:26:4

aellspco Summary of Adverse Events by Body System and Trial Treatment
Serious Adverse Events
Protocol(s): I16216F
Analysis: SAFETY Center: ALL CENTERS

Body System/ Adverse Event	ARIMIDEX ALONE N = 104 No. (%)	ARIMIDEX PLUS HERCEPTIN N = 103 No. (%)
METABOLISM AND NUTRITION DISORDERS		
Total Pts With at Least one AE	-	4 (4)
HYPERCALCAEMIA	-	2 (2)
DEHYDRATION	-	1 (<1)
HYPONATRAEMIA	-	1 (<1)
Total Number of AEs	-	4
CARDIAC DISORDERS		
Total Pts With at Least one AE	1 (<1)	2 (2)
MYOCARDIAL INFARCTION	1 (<1)	1 (<1)
MYOCARDIAL ISCHAEMIA	-	1 (<1)
Total Number of AEs	1	2
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total Pts With at Least one AE	1 (<1)	2 (2)
ARTHRALGIA	1 (<1)	-
BACK PAIN	-	1 (<1)
PATHOLOGICAL FRACTURE	-	1 (<1)
Total Number of AEs	1	2
VASCULAR DISORDERS		
Total Pts With at Least one AE	-	3 (3)
HYPERTENSION	-	1 (<1)
HYPOTENSION	-	1 (<1)
VENOUS INSUFFICIENCY	-	1 (<1)
Total Number of AEs	-	3
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts With at Least one AE	1 (<1)	1 (<1)
FEBRILE NEUTROPENIA	1 (<1)	1 (<1)
Total Number of AEs	1	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Total Pts With at Least one AE	-	2 (2)
CERVIX CARCINOMA	-	1 (<1)
ENDOMETRIAL CANCER	-	1 (<1)
Total Number of AEs	-	2
RENAL AND URINARY DISORDERS		
Total Pts With at Least one AE	1 (<1)	1 (<1)
RENAL FAILURE ACUTE	1 (<1)	-
URINARY RETENTION	-	1 (<1)
Total Number of AEs	1	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	1 (<1)	1 (<1)
DYSPNOEA	1 (<1)	1 (<1)
Total Number of AEs	1	1
EAR AND LABYRINTH DISORDERS		
Total Pts With at Least one AE	-	1 (<1)
MIDDLE EAR INFLAMMATION	-	1 (<1)
Total Number of AEs	-	1
HEPATOBILIARY DISORDERS		
Total Pts With at Least one AE	-	1 (<1)
CHOLELITHIASIS	-	1 (<1)
Total Number of AEs	-	1
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	-	1 (<1)
HEADACHE	-	1 (<1)
Total Number of AEs	-	1
PSYCHIATRIC DISORDERS		
Total Pts With at Least one AE	-	1 (<1)
DEPRESSION	-	1 (<1)
Total Number of AEs	-	1

Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Note: For patients from the Arimidex Alone arm who switched to Herceptin, only AEs before the 1st Herceptin administration are
displayed
AE11 23JUN2006:18:26:4

Cardiotoxicity

Patients entering the study were required to have an LVEF of > 50% at baseline. Cardiac function monitoring was performed at week 9, the beginning of month 5, and every 4 months thereafter until the end of the main study (24 months). In the extension phase of the trial, cardiac function monitoring was performed every 4 months. The cardiac function monitoring was mainly composed of LVEF measurements by echocardiogram or MUGA. The protocol recommended that trastuzumab treatment be discontinued if, during treatment, a fall in LVEF of ≥ an absolute 15% from the baseline value to the LVEF value below 50% were observed, and these asymptomatic cardiac functional abnormalities could be confirmed with a second assessment 3 weeks later.

Summary of Patients with an LVEF Decrease by at least an Absolute 15% from the Baseline and the Absolute LVEF Value below 50%, Safety Population (Before Crossover)

	Anastrozole alone n = 104	**Anastrozole plus Herceptin n = 103**
Symptomatic CHF	0 [a]	1 (<1%)
Confirmed LVEF drops of ≥ 15% from baseline and below 50%	0 [b]	1 (<1%)
At least one LVEF drop of ≥ 15% from baseline and below 50%	0 [c]	6 (5.8%)
[a] One patient experienced symptomatic CHF after cross over to Herceptin-containing regimen following progression [b] Two patients experienced confirmed LVEF drops after cross over to Herceptin-containing [c] Four patients experienced one LVEF drop after cross over to Herceptin-containing regimen,		

In study BO16216, 3 patients were reported to have serious cardiac disorders (myocardial infarction or myocardial ischemia, one in the anastrozole-alone group and 2 in the anastrozole-plus-trastuzumab group), the patient who had myocardial infarction in the anastrozole-alone group died.

A total of 5 patients in the anastrozole-plus-trastuzumab group prematurely discontinued study treatment because of cardiac disorders, 2 with cardiac failure, 2 with cardiotoxicity, and one with myocardial infarction. Three of the 4 patients who prematurely discontinued study treatment due to cardiac failure or cardiotoxicity had an asymptomatic LVEF drop below 50%, and one patient did not have an LVEF determination at the time the study treatment was discontinued.

Of 104 patients from the anastrozole-alone arm, 58 started the trastuzumab regimen after progression of disease was assessed by the investigator during the main phase and extension phase of the study and entered or continued in the extension phase. For two (Patients 1704 and 1705) of the 58 patients who crossed over, minimal information was available on exposure and they were excluded from the exposure table, but were included in the safety results. An additional 15 patients started trastuzumab after they left the study (information was recorded during the survival follow-up phase) and their data are not captured in the after crossover safety outputs. Altogether 73 patients crossed over.

For the 56 patients with available dosing information, the median treatment duration was 21 weeks, with a median of 20 trastuzumab infusions. Cumulative median dose was 3034 mg. trastuzumab exposure was slightly lower in patients who crossed over compared to patients originally randomized to the combination treatment arm, probably because they received trastuzumab as their second line treatment with generally poorer prognosis and shorter time to the next progression.

For patients who crossed over from the anastrozole-alone arm during the main phase of the study, the most frequent AEs (more than 4 patients) were diarrhoea (14%), alopecia (10%), nausea (9%), and vomiting (9%). A total of 8 patients experienced 8 SAEs. One patient died (event of Sudden death) after crossover.

Laboratory findings

Haematological abnormalities have been associated with the use of trastuzumab. A higher proportion of patients in the anastrozole-plus-trastuzumab therapy arm than in the anastrozole-alone arm experienced decreased haemoglobin of at least one NCI-CTC grade during treatment (41 patients

versus 10 patients). Thirty-seven patients in the combination arm experienced a minor shift of one grade to no greater than grade 2 of the NCIC-CTC criteria. Two patients (33313/8133 and 33814/3431) had a shift from grade 2 to grade 3. One patient (29130/2302) had a shift from grade 1 to grade 3. Patient 33333/8442 was reported as having a shift from grade 0 to grade 4. At month 15 her haemoglobin was 13 g/dL, this was recorded as 5.86 g/dL at month 17 and subsequently returned to 12 g/dL by month 19. The investigator commented that this was tumour related.

Except for these abnormalities, there was no evidence of other major safety concerns of clinical significance that were clearly related to the use of trastuzumab in patients with HER2-over-expressed and ER- and/or PgR-positive metastatic breast cancer. There were no clinically relevant changes in vital signs.

3. OVERALL CONCLUSION AND Benefit-risk assessment

The MAH has now submitted documentation to extend the indication of Herceptin to the treatment of HER2-positive and estrogen and/or progesterone receptor positive metastatic breast cancer in combination with an aromatase inhibitor in postmenopausal women. Treatment of this patient population is challenging since two regimens compete: Herceptin + taxane vs aromatase inhibitors.

In support of the extension of indication the MAH has submitted data from the TAnDEM trial, where Herceptin + anastrozole is compared to anastrozole. The choice of the comparator although debated is found to be acceptable. The choice of Herceptin + taxane vs Herceptin + aromatase inhibitor should remain in the discretion of the physician.

The study has shown a difference in progression free survival. Median progression free survival was 2.4 months in the anastrozole group and 4.8 months in the anastrozole plus trastuzumab group. Efficacy results were consistent in clinically relevant subgroups.
There was no statistically significant effect on overall survival (OS), other secondary endpoints such as tumor response rate, clinical benefit rate (stable disease for ≥ six months or complete response or partial response) and time to progression. The lack of significance in OS has to be considered in light of the high cross-over rate to Herceptin, which is understandable from a clinical perspective.

The Applicant has not measured Quality of Life. However, it can be considered that the Quality of Life with Hercetin treatment in the metastatic setting is already established as demonstrated by the taxanes combination studies. The adverse event profile compares favourably to the taxanes +Herceptin regimens evaluated before.

Another issue discussed at the CHMP was the feasibility to extrapolate from anastrozole to aromatase inhibitors in general. The MAH showed a post hoc analysis of the HERA trial where patients with hormone-receptor positive tumors were also included and treated with aromatase inhibitors. The hazard ratio for PFS was comparable for this subgroup to the whole trial. However, from this trial it is also clear that there is a higher rate of all AE and treatment related AE in the trastuzumab plus anastrozole group. The MAH has also cited data from a small phase II trial (n=33) which used trastuzumab in combination with letrozole. These data appear comparable to the Tandem trial with respect to response rate and time to progression. It can be agreed with the MAH that anastrozole and letrozole are used interchangeably. The situation is less clear for steroidal aromatase inhibitors such as exemestane. However, another trial in this setting would be difficult to perform. The “Electra” trial (comparison with letrozole) had to be stopped because of poor enrollment.

A restriction to primary metastatic disease manifestation is not covered by the clinical trial, where most patients were metastatic after a primary localised disease. A restriction to secondary metastatic disease would effectively force the physician to use trastuzumab in combination with docetaxel in patients with secondary metastatic disease. As outline above and as there are no data on the comparison of paclitaxel plus trastuzumab versus aromatase inhibitor plus trastuzumab the decision which combination to use should be left at the discretion of physician and patient.

An important point in the overall benefit/risk assessment is the intended patient population, whose characteristics are likely to be subject to major changes: Trastuzumab is now indicated already in the early breast cancer setting. The benefit and risk of re-treatment upon diagnosis of metastatic disease is currently unknown and due to the current evolution of the knowledge on Herceptin it could not have been possible to be addressed in this study. As no data on re-tretment with Herceptin are available, therefore the treatment should also be restricted to trastuzumab naïve patients. Currently a clinical trial is initiated to study re-treatment and the MAH is committed to report the results as soon as availble.

Trastuzumab and anastrozole each have a well known safety profile. Foremost issue with trastuzumab is cardiotoxicity which does not appear to be more frequent in the studied population in combination with anastrozole than in previous studies with trastuzumab. Anastrozole has a well described effect on bone, there is a higher frequency of fractures in the trastuzumab plus anastrozole group that needs to be elucidated as this may have an influence on the quality of life in these very ill patients.

No additional new or unexpected safety issue due to the combination of trastuzumab and anastrozole were seen in study BO16216. Some minor inconsistencies were noted in the event reporting, however, these inconsistencies do not change the general assessment that risk with combination therapy appears not more than additive.
As regards cardiotoxicity, once entering the extension phase, patients were followed up until subsequent disease progression. Patients had a safety follow up 28 days after their last dose of treatment. The cardiotoxicity could manifest after the safety follow up 28 days after their last dose of treatment. See SmPC if further follow-up is needed.
The Risk Management Plan was revised and included in the subsequent PSUR (submission date: May 24, 2007). It contained both changes resulting from filing study BO16216 (Tandem), and those required as follow-up measurement (FUM) to the indication as adjuvant treatment of early breast cancer.

Benefit/Risk Assessment
Herceptin in combination with anastrozole treatment met the primary endpoint of the study, progression-free survival. While a statistically significant effect on overall survival could not be shown with the planned analysis which included in the Anastrozole arm the patients that crossed-over to Herceptin-containing regimen after progression, a post-hoc analysis suggested an overall survival benefit for patients who received the combination of Herceptin and anastrozole either upfront or after cross-over compared to patients treated with anastrozole alone. Although no quality of life data are available it can be considered that the quality of life of metastatic patients treated with Herceptin is well known and the safety profile compares favourably with a taxane containing regimen. In principle, the proposed indication might provide an alternative to more toxic chemotherapy (e.g. docetaxel) in combination with trastuzuamb.
While currently there might be a patient group not yet having received adjuvant Herceptin treatment, thus representing a potential target population for this indication, the situation might change in some years when most patients have already been pre-treated with Herceptin. Retreatment with the combination of trastuzumab and an aromatose inhibitor when the diseases progresses, following discontinuation of these agents, has not been investigated.
The extrapolation of anastrozole treatment to the claim “in combination with an aromatase inhibitor” is appropriate.
No additional new or unexpected safety issue due to the combination of trastuzumab and anastrozole were seen in study BO16216l. The risk with combination therapy appears not more than additive
Therefore, the benefit/ risk of Herceptin in combination with an aromatase inhibitor for the treatment of patients with HER2-positive and hormone receptor positive metastatic breast cancer, not previously treated with trastuzumab, is positive.

4. CONCLUSION

- On 22 March 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 (see Letter of Undertaking attached to this report):

Area[1]	Description	Due date[2]
	Data on re-treatment from the on-going trial WO17299 (RHEA) "Phase II study of Herceptin alone or in combination with a taxane, as a first-line treatment for patients with metastatic breast cancer, who have relapsed after receiving Herceptin in the adjuvant setting for HER2 positive early breast cancer" will be provided. The results of this ongoing trial will be included in the RMP when they become available, currently estimated in 2010.	2Q 2010
	Update of the Risk Management Plan (RMP): As agreed, the revised RMP will be appended to the next PSUR (planned submission date: May 24, 2007). It will contain both changes resulting from filing study BO16216 (Tandem), and those required as follow-up measurement (FUM) to the HERA filing.	24 May 2007

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.