Clinical Study Report Synopsis

Drug Substance	Fulvestrant (ZD9238)
Study Code	D6990C00001 (ABCSG 21)
Edition Number	1
Date	5 November 2009

A randomised Phase II Study comparing anastrozole and fulvestrant to anastrozole for adjuvant treatment of postmenopausal patients with early breast cancer and disseminated tumour cells in bone marrow - ABCSG 21

Study dates: First subject enrolled: 24 April 2006
Last subject last visit: 15 January 2009 (study closed prematurely).

Phase of development: Therapeutic exploratory (II)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this study report.

Abbreviation or special term	Explanation
ABCSG	Austrian Breast Cancer Study Group
AE	Adverse event
BM	Bone marrow
BMA	Bone marrow aspiration
CSR	Clinical Study Report
CTCAE	Common terminology criteria for adverse events
DTC	Disseminated tumour cells (a surrogate marker of metastases in the bone).
ER	Oestrogen receptor
im	Intramuscular
MedDRA	Medical dictionary for regulatory activities
N	Number
NCI	National Cancer Institute
po	Orally
PgR	Progesterone receptor
PT	Preferred term
WHO	World Health Organisation

This Clinical Study Report (CSR) synopsis is the final study report for Study D6990C0001 (ABCSG21), which was terminated prematurely due to a higher than expected rate of screening failures leading to poor patient recruitment rates. The study was closed on 28 May 2009 at which point all patients ongoing study treatment were discontinued from the study. This report summarises the efficacy and safety data collected up until the premature closure of the study; no data were collected after study closure.

Study centre(s)

Prior to premature termination of the study, 13 patients were recruited from centres in 3 countries (Austria, Germany and Norway).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary and secondary objectives and related outcome variables are summarised in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To compare the frequency of events (ie, presence of DTC in bone marrow BM, clinical recurrence and/or death) in patients treated with anastrozole-fulvestrant combination as compared to that in patients treated with anastrozole alone by assessment of the BM status (ie, the presence or absence of DTC) and the occurrence of clinical recurrences and/or deaths after 12 months (with a diagnostic window of ±3 weeks) of randomised treatment.	Frequency of events (DTC-positive BM specimens, clinical recurrence, death) after 12 months of randomised treatment	Efficacy
Secondary	**Secondary**	
To assess the safety of the anastrozole-fulvestrant combination by evaluation of the rate of NCI CTCAE grade 3 and 4 adverse events (AE) and serious AE (SAE) after 12 and 24 months (with a diagnostic window of ±3 weeks) of randomised treatment. All adverse events will be recorded.	Frequency of NCI CTCAE Version 3 grade 3 or 4 AEs, and SAEs after 12 and 24 months of randomised treatment.	Safety

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
To compare the frequency of events (ie, presence of DTC in BM, clinical recurrence and/or death) in patients treated with anastrozole-fulvestrant combination as compared to that in patients treated with anastrozole alone by assessment of the BM status (ie, the presence or absence of DTC) and the occurrence of clinical recurrences and/or deaths after 24 months (with a diagnostic window of ±3 weeks) of randomised treatment.	Frequency of events (DTC-positive BM specimens, clinical recurrence, death) after 24 months of randomised treatment.	Efficacy

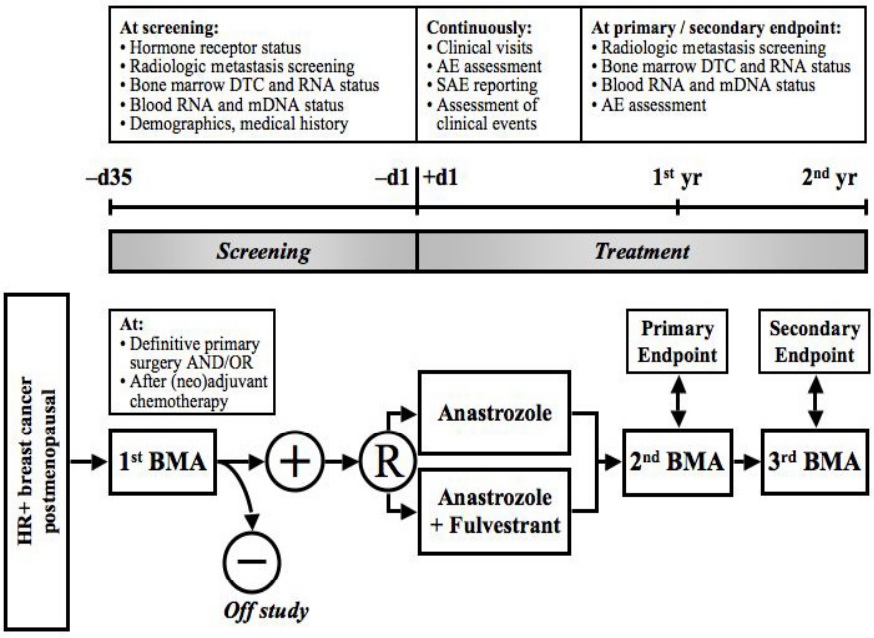
BM:Bone marrow; DTC: Disseminated tumour cells (a surrogate marker of metastases in the bone); NCI:National Cancer Institute; CTCAE:Common terminology criteria for adverse events.

Study design

This was planned as a multicentre, open-label, randomised phase II trial in postmenopausal patients with hormone-receptor positive, non-metastatic primary breast cancer with disseminated tumour cells (DTC) in bone marrow (BM), to compare the efficacy of anastrozole + fulvestrant combination in eliminating DTC to that of anastrozole alone.

The protocol for this study was subject to a peer review according to AstraZeneca and ABCSG standard procedures. Figure 1 displays a brief overview of the study design.

Figure 1 Study design



AE:Adverse event; SAE:Serious adverse event; HR:Hormone receptor; BMA:Bone marrow aspiration; R:Randomisation; d:Day.

Target patient population and sample size

The target patient population was postmenopausal women with hormone-receptor positive, non-metastatic primary breast cancer with DTC in BM.

It was planned that between 600 and 1000 patients (50 to 300 in each country) would be screened for the presence of DTC. Of those with DTC, approximately 176 would subsequently be randomised (allowing for 26% dropouts) to detect, with a 2-sided α=0.05, a 75% reduction in DTC-positive cases with / without clinical evidence of any disease recurrence or death during 12 months of anastrozole-fulvestrant treatment and a 50% reduction DTC-positive cases with / without clinical evidence of any disease recurrence or death during 12 months of anastrozole treatment. DTC-negative patients were to be excluded from the trial: they were to leave the trial immediately after screening and assessment of a DTC-negative BM result.

The study was closed prematurely due to a higher than expected screening failure rate leading to poor patient recruitment rates. Between 24 April 2006 and study termination on 28 May 2009, 13 patients were recruited and randomised. Two hundred and sixty-six patients were screened for study entry but failed inclusion/exclusion criteria or did not meet registration criteria.

Investigational product and comparator(s): dosage and mode of administration

AstraZeneca supplied the following study drugs:

- Fulvestrant (FASLODEX™) as a 5% w/v solution in clear neutral glass pre-filled syringes. Each syringe contained 250 mg of fulvestrant in 5 ml (Formulation Number F6521). The constituents of the solution were as follows: fulvestrant, ethanol 96%, benzyl alcohol, benzyl benzoate and castor oil.

- Anastrozole (ARIMIDEX™) 1 mg white film coated tablets (Formulation Number F11292). The constituents of each tablet were as follows: anastrozole, lactose monohydrate, macrogol, magnesium stearate, hypromellose, povidone, sodium starch glycollate and titanium dioxide.

Eligible patients were randomised to receive either:

- fulvestrant 500 mg regimen (given as two 5 ml im injections, one in each buttock, on Days 0, 14, 28 and every 28 (±3) days thereafter) plus anastrozole 1 mg po once daily (referred to hereafter as fulvestrant + anastrozole)

  or

- anastrozole 1 mg po once daily.

Duration of treatment

It was planned that patients would receive treatment for 24 months or until any of the pre-defined criteria for treatment discontinuation were met. An end-of-study-treatment visit was scheduled for 27 months (±4 weeks) after the start of randomised treatment (3 months [±4 weeks] after completed the protocol defined treatment period).

Statistical methods

For the analysis of the primary endpoint, DTC negative patients who were alive with no clinical recurrence after 12 months would be considered to be "successes". Patients who fell into any of the following categories were not considered as "successes":

- DTC positive with presence of clinical recurrence and/or death (from any cause),
- DTC positive with absence of clinical recurrence or death (from any cause),
- DTC negative with presence of clinical recurrence and/or death (from any cause).

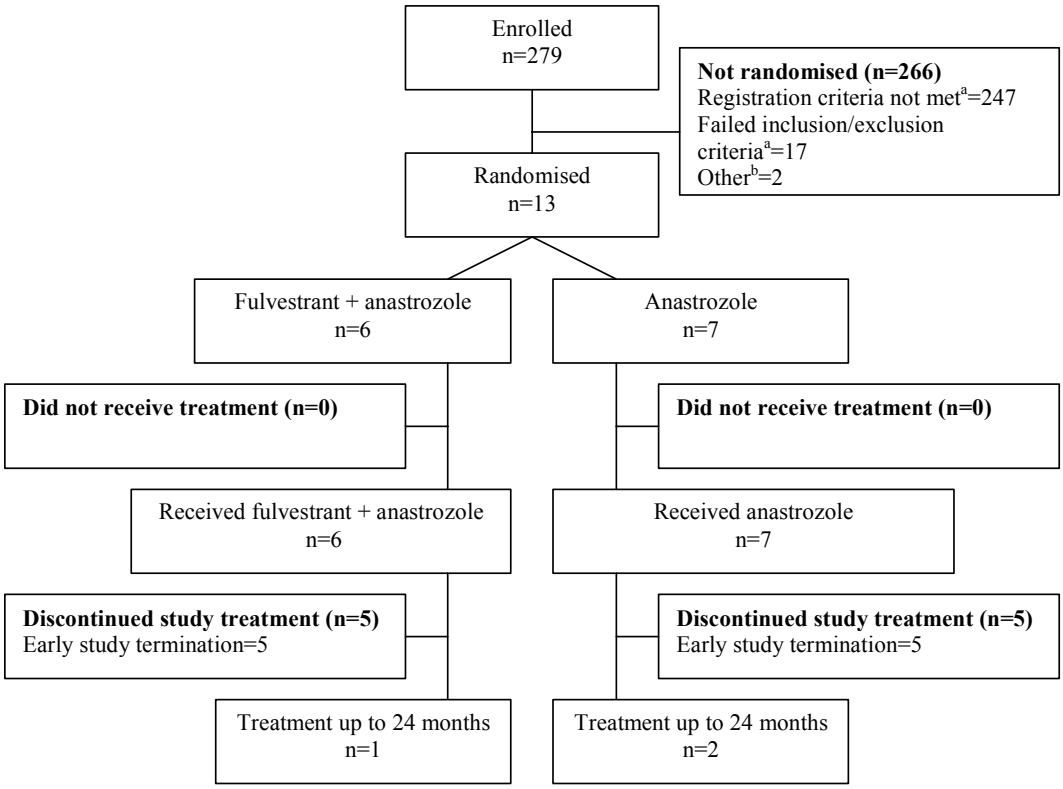
It was planned that a logistic regression analysis, including treatment factor only, would be used to compare the proportion of "successes" between the two treatment groups. The results of the analysis were to be presented in terms of odds ratios together with associated confidence intervals and 2-sided p-values. The estimate of the difference in the "success" rates and the corresponding 2-sided 95% confidence intervals were also to be presented.

As the study was terminated prematurely, these pre-defined formal statistical analyses were not performed.

Patient disposition and demography

Figure 2 summarises the disposition of patients enrolled into the study.

Figure 2 Summary of patient disposition



[a] Two-hundred and forty-seven patients were excluded from the study because they did not meet registration criteria. In addition to this, some patients who were excluded from the study because they failed inclusion/exclusion criteria also failed registration criteria. Overall, reasons for failing registration criteria were (not mutually exclusive): wrong tumour stage (n=5), not ER+ve and/or PgR+ve (n=33), presence of distant metastasis (n=4), not DTC positive (n=262).

[b] Patient 101046 did not complete all pages for screening due to withdrawal. Patient 101009 met all entry criteria but was not randomised due to uncertainty regarding tumour grade (metastases).

ER:Oestrogen receptor; PgR:Progesterone receptor.

A total of 279 patients were enrolled in the study. There was a higher than expected rate of screening failures, therefore, only 13 patients were actually randomised. The most common reason given for screening failure was that registration criteria were not met (247 patients), in particular the absence of DTC at screening. Overall, 93.9% (262/266) of patients screened were not DTC positive at baseline. The observed level of patients who were DTC positive during screening (6.1%) was much lower than the anticipated level of approximately 20% used to estimate the rate of screening failures due to DTC, prior to commencing patient recruitment.

All patients who were randomised went on to receive study treatment (6 patients in the fulvestrant + anastrozole group, 7 patients in the anastrozole group). A total of 3 patients completed the protocol-defined 24-month treatment period. All 10 patients who discontinued study treatment did so due to premature termination of the study.

Table 1 summarises the demographic characteristics at baseline for patients who were randomised to receive study treatment.

Table 1 Demographic characteristics: Full Analysis Set

Demographic characteristic	Fulvestrant + anastrozole N=6	Anastrozole N=7
Sex, n (%)		
Female	6 (100.0)	7 (100.0)
Age, years		
Mean (sd)	60.5 (5.4)	63.4 (3.5)
Median	61	63
Range	53–66	58–69
Weight (kg)		
Mean (sd)	71.5 (11.1)	73.1 (17.8)
Median	69.6	71
Range	61-90	47-100
Race, n (%)		
Caucasian	6 (100.0)	7 (100.0)
WHO performance status at baseline		
0	5 (83.3)	7 (100.0)
1	1 (16.7)	0

n:Number; sd:Standard deviation; WHO:World Health Organisation.

Summary of efficacy results

Table 2 summarises data for the primary endpoint (the frequency of events [DTC-positive BM specimens, clinical recurrence, death] after 12 months) for those patients who were randomised to receive study treatment.

Table 2 Summary of number of patients event free at 12-months: Full Analysis Set

	Fulvestrant + anastrozole N=6	Anastrozole N=7
Patients event free at 12 months	6 (100.0)	7 (100.0)
Not event free at 12 months	0	0
Death (any cause)	0	0
DTC +ve at 12 months	0	0
Clinical disease recurrence	0	0

N:Number; DTC:Disseminated tumour cells.

All 13 patients who were randomised to receive study treatment remained event free at 12 months (6 patients in the fulvestrant + anastrozole, 7 patients in the anastrozole group).

As the study was terminated prematurely, no formal statistical analyses were performed for any efficacy endpoints. The low number of patients randomised to receive treatment prior to premature study closure mean it is not possible to draw meaningful conclusions from the available efficacy data.

Summary of safety results

A summary of AEs in each category, for the 13 patients who received study treatment, is provided in Table 3. The most common AEs (reported by ≥2 patients) by medical dictionary for regulatory activities (MedDRA) preferred term (PT) are summarised in Table 4.

Table 3 Summary of number (%) of patients who had at least 1 AE in any category: Safety Analysis Set

AE category	Number (%) of patients	
	Fulvestrant + anastrozole N=6	Anastrozole N=7
Any AE	5 (83.3)	6 (85.7)
Any causally-related AE[a]	5 (83.3)	4 (57.1)
Any SAE[b]	1 (16.7)	2 (28.6)
Any causally-related SAE[a, c]	0	0
Any AE leading to discontinuation of treatment (DAE)	0	0
Any causally-related DAE[a, c]	0	0
Any AE of CTCAE grade 3 or higher	2 (33.3)	1 (14.3)
Any causally-related AE of CTCAE grade 3 or higher[a, c]	1 (16.7)	0
Any AE with outcome of death	0	0
Any causally-related AE with outcome of death[a]	0	0

[a] In the opinion of the investigator.
[b] Including those with an outcome of death.
[c] Causality to study treatment: specific causality to fulvestrant or anastrozole was not collected in the fulvestrant + anastrozole group.

AE:Adverse event; CTCAE:Common terminology criteria for adverse events; SAE Serious adverse events; DAE:Adverse event leading to discontinuation.

Table 4 Summary of most commonly reported AEs by PT (cut-off ≥2 patients in either treatment group or overall): Safety Analysis Set

MedDRA PT	Number (%) of patients	
	Fulvestrant + anastrozole N=6	Anastrozole N=7
Arthralgia	2 (33.3)	2 (28.6)
Flushing	2 (33.3)	1 (14.3)
Insomnia	3 (50.0)	0
Unevaluable event[a]	2 (33.3)	1 (14.3)
Anorexia	2 (33.3)	0
Constipation	1 (16.7)	1 (14.3)
Fatigue	1 (16.7)	1 (14.3)
Headache	1 (16.7)	1 (14.3)
Hot flush	1 (16.7)	1 (14.3)

[a] Verbatim investigator text did not code to a MedDRA PT. The verbatim text reported by the investigators for these 3 AEs were: 'hypertonia' (patient 101005), 'infection UVI' (patient 301011), 'pain/stiffness in her hands; and pain in her left shoulder in the morning' (patient 302007).

AEs are sorted by overall incidence in the patient population then alphabetically.
AE:Adverse event; MedDRA:Medical dictionary for regulatory activities; PT:Preferred term.

Overall, the most commonly reported AEs in each treatment group were insomnia in the fulvestrant + anastrozole group (3 [50.0%] patients) and arthralgia in the anastrozole group (2 [28.6%] patients). Considering the very low patients numbers, the incidence of AEs was well balanced between the treatment groups.

A total of 3 patients reported an AE of CTCAE (common terminology criteria for adverse events) grade 3 or higher:

- [redacted] in the anastrozole group reported goitre and haemorrhoids, each with a maximum CTCAE grade of 3.
- [redacted] in the fulvestrant + anastrozole reported varicose vein with a maximum CTCAE grade of 3.
- [redacted] in the fulvestrant + anastrozole group reported an 'infection UVI' (verbatim investigator text) with CTCAE grade 3. The investigator text for this AE did not code to a MedDRA PT.

Three patients experienced a total of 5 SAEs (1 patient in the fulvestrant + anastrozole group, 2 patients in the anastrozole group). Table 5 summarises key information for SAEs.

Table 5 Summary of SAEs: Safety Analysis Set

Treatment group	Patient number	Age (years)[a]	Episode term as reported by the investigator	AE (PT)	Criteria for AE seriousness met	Time from start of treatment to AE meeting criteria for seriousness (days)	Causality[b] with the study treatment	Outcome
Fulvestrant + anastrozole	[redacted]	[redacted]	Varicosis both legs	Varicose Vein	Hospitalisation[c]	328	No	No longer present, no residual effects
Anastrozole	[redacted]	[redacted]	Haemorrhoidal surgery	Haemorrhoids	Hospitalisation[c]	182	No	No longer present, no residual effects
			Nodular goiter	Goitre	Hospitalisation[c]	771	No	No longer present, no residual effects
	[redacted]	[redacted]	Renal insufficiency	Renal failure	Hospitalisation[c]	139	No	No longer present, no residual effects
			Lumboischialgia	Sciatica	Hospitalisation[c]	496	No	No longer present, no residual effects

[a] At randomisation.
[b] As assessed by the investigator.
[c] In-patient hospitalisation or prolongation of existing in-patient hospitalisation.
AE:Adverse event; PT:Preferred term; SAE:Serious adverse event.