AstraZeneca

Clinical Study Report

Drug Substance	ICI 182,780 (Fulvestrant)
Study Code	9238IL/0062 (D6995C00004)
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Date	30 September 2010

An open, multicentre Phase I clinical study to assess the tolerability of fulvestrant 500 mg in postmenopausal women with hormone receptor positive advanced or recurrent breast cancer

Study dates: First patient enrolled: 1 April 2004
Last patient completed: 11 June 2010

Phase of development: Phase I

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event
CSR	Clinical study report
CTC	Common Toxicity Criteria
ER	Estrogen receptor
ICH	International Conference on Harmonisation
LD	Loading dose
MedDRA	Medical Dictionary for Regulatory Activities Terminology: A dictionary of internationally common terminology prepared in ICH to conduct the international exchange of medical information rapidly and accurately
SAE	Serious adverse event
SOC	System organ class
250 mg + loading dose (LD) regimen	An initial dose of Fulvestrant 500 mg (2 x 5 ml injections) is intramuscularly administered on Day 0, followed by 250 mg (1 x 5 ml injection) on Days 14, 28 and then every 28 days.
500 mg regimen	Fulvestrant 500 mg (2 x 5 mL injections) is intramuscularly administered on Days 0, 14, 28 and then every 28 days.
Assessment	An observation made on a variable involving a subjective judgement (assessment)
Co-ordinating investigator	The Investigator co-ordinating the investigators and/or activities.
Investigator(s)	Principal investigator and subinvestigator in the protocol
Parameter	A quantity (usually unknown) that characterizes the distribution of a variable in a population of patients.
Principal investigator	A person responsible for the conduct of a clinical study at an investigational study site. Every investigational study site has a principal investigator.
Variable	A characteristic or a property of a patient that may vary e.g., from time to time or between patients

1. INTRODUCTION

Fulvestrant is an antiestrogen with a mechanism of action to downregulate the estrogen receptor (ER), and also like tamoxifen, it competitively blocks estrogen on the ER (Morris C and Wakeling A). Pharmacology studies in rats and monkeys have shown that fulvestrant has no agonist activity, which is the problem of antiestrogens such as tamoxifen. With a mechanism of action and lacking cross-resistance with existing drugs, fulvestrant is expected to be used as an endocrine therapy drug for postmenopausal advanced or recurrent breast cancer.

This study was an open, multicentre clinical study to assess the safety tolerability of 500 mg fulvestrant in Japanese postmenopausal women with hormone receptor positive, advanced or recurrent breast cancer.

A total of 20 patients from 6 centres in Japan were enrolled into the study (10 patients into the Step 1 and 10 patients into the Step 2). The first patient was enrolled on 1 April 2004 and the date when the last patient completed the study was 11 June 2010.

2. SCOPE OF THIS ADDENDUM

The clinical study report (CSR) for study D6995C00004 for primary analysis was published on 6 December 2006 based on a cut-off date of 28 February 2006. This addendum has been prepared to provide safety data after this date for the 6 patients (3 patients into the Step 1 and 3 patients into the Step 2) who continued in the study after data cut-off.

3. RESULTS

3.1 Disposition

All 6 patients who remained in the study after 28 February 2006 have discontinued the study due to disease progression (see Listing 12.2.1.1.1).

3.2 Protocol deviations

The number of patients with important protocol deviations in each treatment regimen are summarised in Table 11.1.3. All individual patients with important protocol deviations are listed, by centre, in Listing 12.2.2.

There were no important protocol deviations, which leaded to exclusion from safety analysis set (see Table 11.1.4).

3.3 Use of concomitant medication and treatment compliance

3.3.1 Concomitant medication after study entry

In common with the data for the study population reported in the CSR, a wide variety of concomitant medications were taken throughout the study by the patients included in this addendum (see Listing 12.2.4.4); however, they were not considered to have interfered with the specific safety assessments reported in this addendum.

Overall, the concomitant treatment administered was representative of that routinely prescribed for patients with advanced or recurrent breast cancer.

3.3.2 Treatment compliance

In general, fulvestrant was administered at the medical centres according to the protocol although some dose delays due to patient's visit schedule were reported in two patients.

3.4 Efficacy and pharmacokinetic results

No data for efficacy and pharmacokinetic were collected after data cut-off.

3.5 Safety results

The safety data presented in this addendum are mainly focused on data for the 6 patients who remained in the study following 28 February 2006 (date of data cut-off).

3.5.1 Extent of exposure

Exposure to study treatment is listed in Listing 12.2.5.1.

Median treatment duration was 253.5 days (range: 43 – 2094 days) in total 20 patients, with 210.5 and 297.5 days in the fulvestrant 250mg + loading dose (LD) regimen and 500 mg regimen, respectively. Median total number of dosing was 10.0 (range: 2 – 76) in total 20 patients, with 8.5 and 11.5 in the fulvestrant 250mg + LD regimen and 500 mg regimen, respectively. Median total number of fulvestrant injection was 9.5 and 23.0 in the fulvestrant 250 mg + LD regimen and 500 mg regimen, respectively (see Table 11.3.1.2, Table 11.3.1.4 and Table 11.3.1.5).

The extent of exposure for 6 patients ongoing in the study after the date of data cut-off is presented in Table 1. There was a remarkable long treatment duration (more than 2000 days) for 2 patients in the fulvestrant 250 mg + LD regimen.

Table 1 Listing of exposure

E-code	Treatment	Date of first injection	Date of last injection at primary analysis	Date of last injection at final analysis	Treatment duration[1)] at primary analysis (days)	Treatment duration[1)] at final analysis (days)
E0001001	250 mg + LD	3-Aug-04	14-Mar-06	30-Mar-10	617	2094
E0006002	250 mg + LD	15-Oct-04	15-Mar-06	16-Apr-10	545	2038
E0001003	250 mg + LD	10-Nov-04	31-Mar-06	28-Mar-08	535	1263
E0007001	500 mg	9-May-05	12-Apr-06	30-Aug-06	367	507
E0004005	500 mg	24-May-05	25-Apr-06	20-Jun-06	365	421
E0001006	500 mg	1-Aug-05	10-Apr-06	18-Jan-08	281	929

1) Treatment duration = (date of last known injection+28) - (date of first dose) + 1
Data derived from Listing 12.2.5.1

3.5.2 Adverse events

All adverse events (AEs) data in this study are listed in Listing 12.2.7.1.

The AEs data following data cut-off do not alter the safety conclusions in the CSR published on 6 December 2006.

3.5.2.1 Categories of adverse events

A summary of AEs in each category is presented in Table 2 and Table 3.

One drug-related AE with worst common toxicity criteria (CTC) grade 3 in one patient was newly reported after data cut-off. The total number of AEs and drug-related AEs increased to 207 and 97, respectively. There were no changes in other categories after data cut-off.

Table 2 Number (%) of patients who had an adverse event in any category (Safety analysis set)

	N (%) of patients who had an adverse event[1)]		
	Fulvestrant 250 mg+LD	Fulvestrant 500 mg	Total
	n=10	n=10	n=20
Any adverse event	10 (100.0)	10 (100.0)	20 (100.0)
Any SAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Any SAE not leading to death	1 (10.0)	0 (0.0)	1 (5.0)
Any AE leading to discontinuation of study treatment	0 (0.0)	0 (0.0)	0 (0.0)

Table 2 Number (%) of patients who had an adverse event in any category (Safety analysis set)

	N (%) of patients who had an adverse event[1)]		
	Fulvestrant 250 mg+LD	Fulvestrant 500 mg	Total
	n=10	n=10	n=20
Any AE with worst CTC grade 3 or 4	5 (50.0)	0 (0.0)	5 (25.0)
Any drug-related AE	9 (90.0)	9 (90.0)	18 (90.0)
Any serious drug-related AE leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Any serious drug-related AE not leading to death	1 (10.0)	0 (0.0)	1 (5.0)
Any drug-related AE leading to discontinuation of study treatment	0 (0.0)	0 (0.0)	0 (0.0)
Any drug-related AE with worst CTC grade 3 or 4	4 (40.0)	0 (0.0)	4 (20.0)

1) Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

LD: Loading Dose, SAE: Serious adverse event
Data derived from Table 11.3.2.1.1, Table 11.3.2.1.2

Table 3 Number of adverse events (Safety analysis set)

	Total number of adverse events[1)]		
	Fulvestrant 250 mg+LD	Fulvestrant 500 mg	Total
	n=10	n=10	n=20
Any AE	139	68	207
Any SAE leading to death	0	0	0
Any SAE not leading to death	1	0	1
Any AE leading to discontinuation of study treatment	0	0	0
Any AE with worst CTC grade 3 or 4	7	0	7
Any drug-related AE	64	33	97
Any serious drug-related AE leading to death	0	0	0
Any serious drug-related AE not leading to death	1	0	1
Any drug-related AE leading to discontinuation of study treatment	0	0	0
Any drug-related AE with worst CTC grade 3 or 4	4	0	4

1) Multiple events in the same category are counted multiple times in that category. Multiple events belonging to more than one category are counted multiple.

LD: Loading Dose, SAE: Serious adverse event
Data derived from Table 11.3.2.2.1, Table 11.3.2.2.2

3.5.2.2 Most common adverse events

All AEs in the study, summarised by Medical Dictionary for Regulatory Activities Terminology (MedDRA, Ver. 13.0) system organ class (SOC), preferred term and worst CTC grade, are presented in Table 4.

The overall AE profile was similar between the fulvestrant 250 mg + LD regimen and 500 mg regimen.

Most of AEs were classified in the SOCs of General Disorders and Administration Site Conditions, Gastrointestinal Disorders, Musculoskeletal Disorders, Infections and Infestations, Nervous System Disorders, and Skin and Subcutaneous Tissues disorders. In a total of 20 patients, the most common AEs (≥ 3 patients) were nasopharyngitis and injection site pain (8 patients each), injection site induration (7 patients), arthralgia (6 patients), injection site pruritus, back pain, and cough (5 patients each), constipation, nausea, decreased appetite, headache, and rash (4 patients each), diarrhoea, fatigue, musculoskeletal stiffness, dizziness, pruritus, and hot flush (3 patients each). There were no new AEs after data cut-off, although the number of AEs increased because the treatment duration of 6 patients was prolonged.

One AE (injection site necrosis) with worst CTC grade 3 was reported in one patient (E0006002) of the fulvestrant 250 mg + LD regimen after data cut-off (See Table 11.3.2.5 and Listing 12.2.7.1).

Table 4 Number (%) of patients who had any adverse event by system organ class, preferred term and worst CTC grade (safety analysis set)

	Fulvestrant 250 mg+LD n=10					Fulvestrant 500 mg n=10					Total n=20				
	Worst CTC grade					Worst CTC grade					Worst CTC grade				
System Organ Class and Preferred Term	1	2	3	4	Total	1	2	3	4	Total	1	2	3	4	Total
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	1	1	2 (20.0)	0	0	0	0	0 (0.0)	0	0	1	1	2 (10.0)
Febrile neutropenia	0	0	1	0	1 (10.0)	0	0	0	0	0 (0.0)	0	0	1	0	1 (5.0)
Neutropenia	0	0	0	1	1 (10.0)	0	0	0	0	0 (0.0)	0	0	0	1	1 (5.0)
EYE DISORDERS	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Conjunctivitis allergic	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
GASTROINTESTINAL DISORDERS	4	2	1	0	7 (70.0)	3	2	0	0	5 (50.0)	7	4	1	0	12 (60.0)
Abdominal discomfort	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Abdominal pain lower	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Abdominal pain upper	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Constipation	2	1	0	0	3 (30.0)	0	1	0	0	1 (10.0)	2	2	0	0	4 (20.0)
Dental caries	1	0	0	0	1 (10.0)	1	0	0	0	1 (10.0)	2	0	0	0	2 (10.0)
Diarrhoea	2	0	1	0	3 (30.0)	0	0	0	0	0 (0.0)	2	0	1	0	3 (15.0)
Flatulence	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)

Table 4 Number (%) of patients who had any adverse event by system organ class, preferred term and worst CTC grade (safety analysis set)

	Fulvestrant 250 mg+LD n=10					Fulvestrant 500 mg n=10					Total n=20				
	Worst CTC grade					Worst CTC grade					Worst CTC grade				
System Organ Class and Preferred Term	**1**	**2**	**3**	**4**	**Total**	**1**	**2**	**3**	**4**	**Total**	**1**	**2**	**3**	**4**	**Total**
Gastritis	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Gingival pain	0	0	0	0	0 (0.0)	0	1	0	0	1 (10.0)	0	1	0	0	1 (5.0)
Nausea	3	0	0	0	3 (30.0)	1	0	0	0	1 (10.0)	4	0	0	0	4 (20.0)
Periodontitis	0	1	0	0	1 (10.0)	0	0	0	0	0 (0.0)	0	1	0	0	1 (5.0)
Stomatitis	1	0	0	0	1 (10.0)	1	0	0	0	1 (10.0)	2	0	0	0	2 (10.0)
Vomiting	2	0	0	0	2 (20.0)	0	0	0	0	0 (0.0)	2	0	0	0	2 (10.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	7	1	1	0	9 (90.0)	7	1	0	0	8 (80.0)	14	2	1	0	17 (85.0)
Asthenia	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Chest pain	1	0	0	0	1 (10.0)	1	0	0	0	1 (10.0)	2	0	0	0	2 (10.0)
Discomfort	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Fatigue	1	0	0	0	1 (10.0)	1	1	0	0	2 (20.0)	2	1	0	0	3 (15.0)
Inflammation	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Injection site discomfort	1	0	0	0	1 (10.0)	1	0	0	0	1 (10.0)	2	0	0	0	2 (10.0)
Injection site erythema	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Injection site haemorrhage	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Injection site induration	4	0	0	0	4 (40.0)	3	0	0	0	3 (30.0)	7	0	0	0	7 (35.0)
Injection site necrosis	0	0	1	0	1 (10.0)	0	0	0	0	0 (0.0)	0	0	1	0	1 (5.0)
Injection site pain	5	0	0	0	5 (50.0)	3	0	0	0	3 (30.0)	8	0	0	0	8 (40.0)
Injection site pruritus	3	0	0	0	3 (30.0)	2	0	0	0	2 (20.0)	5	0	0	0	5 (25.0)
Injection site swelling	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Injection site ulcer	0	1	0	0	1 (10.0)	0	0	0	0	0 (0.0)	0	1	0	0	1 (5.0)
Pyrexia	2	0	0	0	2 (20.0)	0	0	0	0	0 (0.0)	2	0	0	0	2 (10.0)
INFECTIONS AND INFESTATIONS	4	2	0	0	6 (60.0)	2	1	0	0	3 (30.0)	6	3	0	0	9 (45.0)
Cellulitis	0	0	0	0	0 (0.0)	0	1	0	0	1 (10.0)	0	1	0	0	1 (5.0)
Herpes simplex	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Nasopharyngitis	4	1	0	0	5 (50.0)	3	0	0	0	3 (30.0)	7	1	0	0	8 (40.0)
Pharyngitis	1	1	0	0	2 (20.0)	0	0	0	0	0 (0.0)	1	1	0	0	2 (10.0)
Pneumonia mycoplasmal	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Tinea pedis	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2	0	0	0	2 (20.0)	2	0	0	0	2 (20.0)	4	0	0	0	4 (20.0)
Contrast media reaction	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Contusion	1	0	0	0	1 (10.0)	1	0	0	0	1 (10.0)	2	0	0	0	2 (10.0)

Table 4 Number (%) of patients who had any adverse event by system organ class, preferred term and worst CTC grade (safety analysis set)

	Fulvestrant 250 mg+LD					Fulvestrant 500 mg					Total				
	n=10					n=10					n=20				
	Worst CTC grade					Worst CTC grade					Worst CTC grade				
System Organ Class and Preferred Term	**1**	**2**	**3**	**4**	**Total**	**1**	**2**	**3**	**4**	**Total**	**1**	**2**	**3**	**4**	**Total**
Mountain sickness acute	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Procedural pain	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
INVESTIGATIONS	2	0	0	0	2 (20.0)	1	0	0	0	1 (10.0)	3	0	0	0	3 (15.0)
Alanine aminotransferase increased	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Aspartate aminotransferase increased	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Blood alkaline phosphatase increased	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Haemoglobin decreased	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Weight decreased	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
METABOLISM AND NUTRITION DISORDERS	2	1	1	0	4 (40.0)	2	0	0	0	2 (20.0)	4	1	1	0	6 (30.0)
Decreased appetite	2	1	0	0	3 (30.0)	1	0	0	0	1 (10.0)	3	1	0	0	4 (20.0)
Hypercholesterolaemia	1	0	0	0	1 (10.0)	1	0	0	0	1 (10.0)	2	0	0	0	2 (10.0)
Hypertriglyceridaemia	0	0	1	0	1 (10.0)	0	0	0	0	0 (0.0)	0	0	1	0	1 (5.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	4	1	0	0	5 (50.0)	4	2	0	0	6 (60.0)	8	3	0	0	11 (55.0)
Arthralgia	3	1	0	0	4 (40.0)	2	0	0	0	2 (20.0)	5	1	0	0	6 (30.0)
Back pain	2	0	0	0	2 (20.0)	3	0	0	0	3 (30.0)	5	0	0	0	5 (25.0)
Muscular weakness	0	0	0	0	0 (0.0)	0	1	0	0	1 (10.0)	0	1	0	0	1 (5.0)
Musculoskeletal pain	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Musculoskeletal stiffness	1	0	0	0	1 (10.0)	1	1	0	0	2 (20.0)	2	1	0	0	3 (15.0)
Myalgia	0	1	0	0	1 (10.0)	0	0	0	0	0 (0.0)	0	1	0	0	1 (5.0)
Neck pain	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Rheumatoid arthritis	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Tenosynovitis	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
NERVOUS SYSTEM DISORDERS	3	1	0	1	5 (50.0)	4	0	0	0	4 (40.0)	7	1	0	1	9 (45.0)
Carpal tunnel syndrome	0	1	0	0	1 (10.0)	0	0	0	0	0 (0.0)	0	1	0	0	1 (5.0)
Cerebral infarction	0	0	0	1	1 (10.0)	0	0	0	0	0 (0.0)	0	0	0	1	1 (5.0)
Dizziness	1	0	0	0	1 (10.0)	2	0	0	0	2 (20.0)	3	0	0	0	3 (15.0)
Headache	2	0	0	0	2 (20.0)	2	0	0	0	2 (20.0)	4	0	0	0	4 (20.0)
Hypoaesthesia	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Monoplegia	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Sensory disturbance	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
PSYCHIATRIC DISORDERS	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Adjustment disorder	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Insomnia	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)

Table 4 Number (%) of patients who had any adverse event by system organ class, preferred term and worst CTC grade (safety analysis set)

	Fulvestrant 250 mg+LD n=10					Fulvestrant 500 mg n=10					Total n=20				
	Worst CTC grade					Worst CTC grade					Worst CTC grade				
System Organ Class and Preferred Term	**1**	**2**	**3**	**4**	**Total**	**1**	**2**	**3**	**4**	**Total**	**1**	**2**	**3**	**4**	**Total**
RENAL AND URINARY DISORDERS	1	0	0	0	1 (10.0)	1	0	0	0	1 (10.0)	2	0	0	0	2 (10.0)
Dysuria	1	0	0	0	1 (10.0)	1	0	0	0	1 (10.0)	2	0	0	0	2 (10.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3	2	0	0	5 (50.0)	2	0	0	0	2 (20.0)	5	2	0	0	7 (35.0)
Cough	3	1	0	0	4 (40.0)	1	0	0	0	1 (10.0)	4	1	0	0	5 (25.0)
Dyspnoea	0	1	0	0	1 (10.0)	1	0	0	0	1 (10.0)	1	1	0	0	2 (10.0)
Epistaxis	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Oropharyngeal pain	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Throat irritation	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	6	3	0	0	9 (90.0)	1	0	0	0	1 (10.0)	7	3	0	0	10 (50.0)
Alopecia	1	1	0	0	2 (20.0)	0	0	0	0	0 (0.0)	1	1	0	0	2 (10.0)
Erythema	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Ingrowing nail	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Nail disorder	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Pruritus	0	2	0	0	2 (20.0)	1	0	0	0	1 (10.0)	1	2	0	0	3 (15.0)
Rash	3	1	0	0	4 (40.0)	0	0	0	0	0 (0.0)	3	1	0	0	4 (20.0)
Rash papular	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
VASCULAR DISORDERS	2	0	1	0	3 (30.0)	2	0	0	0	2 (20.0)	4	0	1	0	5 (25.0)
Hot flush	2	0	0	0	2 (20.0)	1	0	0	0	1 (10.0)	3	0	0	0	3 (15.0)
Hypertension	0	0	1	0	1 (10.0)	1	0	0	0	1 (10.0)	1	0	1	0	2 (10.0)

A patient experiencing more than one AE within a SOC or preferred term is counted once within the SOC or preferred term.
LD: Loading Dose
Data derived from Table 11.3.2.3

3.5.2.3 Drug-related adverse events

All drug-related AEs in the study, summarised by MedDRA (Ver. 13.0) system organ class, preferred term and worst CTC grade, are shown in Table 5.

The drug-related AE profile was generally similar between the fulvestrant 250 mg + LD regimen and 500 mg regimen.

Most of drug-related AEs were classified in the SOCs of General Disorders and Administration Site Conditions. In total 20 patients, the most common drug-related AEs (≥ 3 patients) were injection site pain (8 patients), injection site induration (7 patients), injection

site pruritus (5 patients), headache, hot flush, and rash (3 patients each). There were no new drug-related AEs after data cut-off, although the number of AEs increased because the treatment duration of 6 patients was prolonged.
One drug-related AE (injection site necrosis) with worst CTC grade 3 was reported in one patient (E0006002) of the fulvestrant 250 mg + LD regimen after data cut-off (See Table 11.3.2.6 and Listing 12.2.7.1).

Table 5 Number (%) of patients who had any drug-related adverse event by preferred term and worst CTC grade (safety analysis set)

	Fulvestrant 250 mg+LD n=10					Fulvestrant 500 mg n=10					Total n=20				
	Worst CTC grade					Worst CTC grade					Worst CTC grade				
System Organ Class and Preferred Term	**1**	**2**	**3**	**4**	**Total**	**1**	**2**	**3**	**4**	**Total**	**1**	**2**	**3**	**4**	**Total**
GASTROINTESTINAL DISORDERS	2	1	0	0	3 (30.0)	1	0	0	0	1 (10.0)	3	1	0	0	4 (20.0)
Abdominal discomfort	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Abdominal pain lower	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Constipation	1	0	0	0	1 (10.0)	1	0	0	0	1 (10.0)	2	0	0	0	2 (10.0)
Flatulence	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Nausea	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Periodontitis	0	1	0	0	1 (10.0)	0	0	0	0	0 (0.0)	0	1	0	0	1 (5.0)
Stomatitis	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	7	1	1	0	9 (90.0)	8	0	0	0	8 (80.0)	15	1	1	0	17 (85.0)
Asthenia	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Chest pain	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Fatigue	0	0	0	0	0 (0.0)	2	0	0	0	2 (20.0)	2	0	0	0	2 (10.0)
Injection site discomfort	1	0	0	0	1 (10.0)	1	0	0	0	1 (10.0)	2	0	0	0	2 (10.0)
Injection site erythema	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Injection site haemorrhage	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Injection site induration	4	0	0	0	4 (40.0)	3	0	0	0	3 (30.0)	7	0	0	0	7 (35.0)
Injection site necrosis	0	0	1	0	1 (10.0)	0	0	0	0	0 (0.0)	0	0	1	0	1 (5.0)
Injection site pain	5	0	0	0	5 (50.0)	3	0	0	0	3 (30.0)	8	0	0	0	8 (40.0)
Injection site pruritus	3	0	0	0	3 (30.0)	2	0	0	0	2 (20.0)	5	0	0	0	5 (25.0)
Injection site swelling	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Injection site ulcer	0	1	0	0	1 (10.0)	0	0	0	0	0 (0.0)	0	1	0	0	1 (5.0)
INFECTIONS AND INFESTATIONS	0	1	0	0	1 (10.0)	0	0	0	0	0 (0.0)	0	1	0	0	1 (5.0)
Herpes simplex	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Nasopharyngitis	0	1	0	0	1 (10.0)	0	0	0	0	0 (0.0)	0	1	0	0	1 (5.0)
INVESTIGATIONS	1	0	0	0	1 (10.0)	1	0	0	0	1 (10.0)	2	0	0	0	2 (10.0)
Blood alkaline phosphatase increased	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)

Table 5 Number (%) of patients who had any drug-related adverse event by preferred term and worst CTC grade (safety analysis set)

	Fulvestrant 250 mg+LD n=10					Fulvestrant 500 mg n=10					Total n=20				
	Worst CTC grade					Worst CTC grade					Worst CTC grade				
System Organ Class and Preferred Term	**1**	**2**	**3**	**4**	**Total**	**1**	**2**	**3**	**4**	**Total**	**1**	**2**	**3**	**4**	**Total**
Haemoglobin decreased	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
METABOLISM AND NUTRITION DISORDERS	0	0	1	0	1 (10.0)	1	0	0	0	1 (10.0)	1	0	1	0	2 (10.0)
Hypercholesterolaemia	1	0	0	0	1 (10.0)	1	0	0	0	1 (10.0)	2	0	0	0	2 (10.0)
Hypertriglyceridaemia	0	0	1	0	1 (10.0)	0	0	0	0	0 (0.0)	0	0	1	0	1 (5.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3	0	0	0	3 (30.0)	0	1	0	0	1 (10.0)	3	1	0	0	4 (20.0)
Arthralgia	2	0	0	0	2 (20.0)	0	0	0	0	0 (0.0)	2	0	0	0	2 (10.0)
Back pain	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Muscular weakness	0	0	0	0	0 (0.0)	0	1	0	0	1 (10.0)	0	1	0	0	1 (5.0)
Musculoskeletal stiffness	1	0	0	0	1 (10.0)	1	0	0	0	1 (10.0)	2	0	0	0	2 (10.0)
NERVOUS SYSTEM DISORDERS	1	1	0	1	3 (30.0)	2	0	0	0	2 (20.0)	3	1	0	1	5 (25.0)
Carpal tunnel syndrome	0	1	0	0	1 (10.0)	0	0	0	0	0 (0.0)	0	1	0	0	1 (5.0)
Cerebral infarction	0	0	0	1	1 (10.0)	0	0	0	0	0 (0.0)	0	0	0	1	1 (5.0)
Dizziness	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Headache	1	0	0	0	1 (10.0)	2	0	0	0	2 (20.0)	3	0	0	0	3 (15.0)
PSYCHIATRIC DISORDERS	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Adjustment disorder	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
Insomnia	0	0	0	0	0 (0.0)	1	0	0	0	1 (10.0)	1	0	0	0	1 (5.0)
RENAL AND URINARY DISORDERS	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Dysuria	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	1	0	0	2 (20.0)	0	0	0	0	0 (0.0)	1	1	0	0	2 (10.0)
Cough	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Dyspnoea	0	1	0	0	1 (10.0)	0	0	0	0	0 (0.0)	0	1	0	0	1 (5.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2	1	0	0	3 (30.0)	0	0	0	0	0 (0.0)	2	1	0	0	3 (15.0)
Nail disorder	1	0	0	0	1 (10.0)	0	0	0	0	0 (0.0)	1	0	0	0	1 (5.0)
Pruritus	0	1	0	0	1 (10.0)	0	0	0	0	0 (0.0)	0	1	0	0	1 (5.0)
Rash	2	1	0	0	3 (30.0)	0	0	0	0	0 (0.0)	2	1	0	0	3 (15.0)
VASCULAR DISORDERS	2	0	1	0	3 (30.0)	1	0	0	0	1 (10.0)	3	0	1	0	4 (20.0)
Hot flush	2	0	0	0	2 (20.0)	1	0	0	0	1 (10.0)	3	0	0	0	3 (15.0)
Hypertension	0	0	1	0	1 (10.0)	0	0	0	0	0 (0.0)	0	0	1	0	1 (5.0)

A patient experiencing more than one AE within a SOC or preferred term is counted once within the SOC or preferred term.
LD: Loading Dose
Data derived from Table 11.3.2.4

3.5.2.4 Deaths, serious adverse events, discontinuation of investigational product due to adverse events, and other significant adverse events

There were no death, serious adverse events, discontinuation of investigational product due to AEs, and other significant adverse events in the 6 patients who continued the study treatment from data cut-off to the last patient completed.

One SAE was reported before data cut-off. The detail of this case is given in the CSR published on 6 December 2006.

3.5.3 Clinical laboratory evaluation

The descriptive statistics of haematology and clinical chemistry variable are shown in Table 11.3.7.1.1 and Table 11.3.7.1.2. A listing of changes in haematology and clinical chemistry parameters over time for individual patients is provided in Listings 12.2.8.1.1 to 12.2.8.1.2, and 12.2.8.2.1 to 12.2.8.2.4.

Shift table of baseline CTC grade vs worst CTC is shown in Table 11.3.7.1.7 and Table 11.3.7.1.8. There was no patient with CTC grade 3 or 4 changes of haematology and clinical chemistry values after data cut-off.

The haematology and clinical chemistry results obtained in the period following 28 February 2006 (date of data cut-off) in those patients who were ongoing in the study and who provided further samples do not alter the conclusions reported in the CSR published on 6 December 2006. There were no clinically relevant changes in laboratory parameters and apparent difference of the effects on clinical laboratory variables between the fulvestrant 250 mg + LD regimen and 500 mg regimen.

3.5.4 Vital signs, WHO performance status and other observations related to safety

3.5.4.1 Vital signs

Changes in pulse rate, and systolic and diastolic blood pressure during the study are presented in Table 11.3.8.1.1. Individual vital signs data are listed in Listing 12.2.9.1.

"Hypertension" reported as AEs in two patients (E0001003 in the fulvestrant 250 mg + LD regimen and E0007001 in the fulvestrant 500 mg regimen) before data cut-off were still present after data cut-off. The worst CTC grade and causality of the AEs were not changed after data cut-off. No other patients had hypertension after data cut-off.

The vital signs data for the patients ongoing in the study during the period following data cut-off through to discontinuation were unremarkable and consistent with previous findings.

3.5.4.2 WHO performance status and other observations related to safety

Changes in mean body weight were shown in Table 11.3.8.1.1, and shift table of WHO performance status was presented in Table 11.3.8.1.3. Individual body weight and WHO performance status data are listed in Listing 12.2.9.1 and Listing 12.2.10.1.

The mean changes in body weight during fulvestrant treatment were small and not clinically significant. No "weight decreased" was reported as an AE after data cut-off.

WHO performance status did not change during the study in the 6 patients who continued the study treatment after data cut-off.

5. REFERENCE LIST

Morris C and Wakeling A
Morris C and Wakeling A. Fulvestrant ('Faslodex') – a new treatment option for patients progressing on prior endocrine therapy. Endocrine-Related Cancer 2002;9:267-276