AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: FASLODEX
ACTIVE INGREDIENT: Fulvestrant

Study No: D6697C00057 (Study 57)
A DOUBLE-BLIND, RANDOMISED, MULTICENTRE TRIAL TO COMPARE THE ANTI-TUMOUR EFFECTS AND TOLERABILITY OF A 500 MG DOSE OF FASLODEX™ (Fulvestrant) PLUS ARIMIDEX™ (Anastrozole), WITH A 500 MG DOSE OF FASLODEX™ ALONE WITH ARIMIDEX ALONE, IN POSTMENOPAUSAL WOMEN PRIOR TO SURGERY FOR PRIMARY BREAST CANCER

Developmental phase: Therapeutic exploratory (II)
Last subject last visit: 06 November 2008
Date of interim efficacy analysis: 30 July 2009
Date of Report: 12 October 2009

This report summarises an interim analysis of the data, performed on 30 July 2009. At the time of writing, tumour samples for 5 patients were still being analysed, therefore, the efficacy data are only summarised. The formal statistical analysis of the final data set will be reported at a later date, when all tumour samples have been analysed.

OBJECTIVES:

The primary and secondary objectives and corresponding outcome variables are summarised in Table 1.

Table 1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To compare the antioestrogenic and antiproliferative effect of a single 500 mg dose of fulvestrant plus 1mg daily of anastrozole given over 14 to 21 days with a 500mg dose of fulvestrant alone, and with 1mg daily of anastrozole given over 14 to 21 days in primary breast tumours.	Oestrogen receptor (ER) index, progesterone receptor (PgR) index and Ki67 labelling index.	Efficacy
Secondary	**Secondary**	
To assess the tolerability of a 500mg dose of fulvestrant plus anastrozole compared with a 500mg dose of fulvestrant alone, with anastrozole alone.	Adverse events (AEs), serious adverse events (SAEs), withdrawals, laboratory parameters.	Safety

METHODS:

This was a double-blind, randomised, multicentre, parallel group study in postmenopausal females with breast cancer, awaiting curative-intent surgery. It was planned that patients would have surgery for breast cancer between 14 and 21 days after completed their randomised treatment.

The study compared 3 treatment groups: fulvestrant 500 mg; fulvestrant 500 mg with anastrozole 1 mg; and anastrozole 1 mg. In the original study protocol, patients were to receive fulvestrant 250 mg. A protocol amendment dated 10 June 2005 changed the dose from 250 mg to a new fulvestrant 500 mg dose regimen that was being investigated in phase III clinical trials at the time.

The analysis was to be performed ‘per protocol’ as the objective was to distinguish between the treatments. The per protocol analysis was to include patients who completed the end of treatment assessment for the primary endpoint and who had no protocol violations and no significant protocol deviations (as assessed by the Principal Investigator).

RESULTS:

Patient disposition and demography

A total of 121 patients were enrolled into the study (39 in the fulvestrant group, 40 in the fulvestrant + anastrozole group, and 42 in the anastrozole group). There were no screening failures. Of the 121 patients enrolled, 99 were included in the interim per protocol analysis reported in this summary. The following patients were excluded from the per protocol analysis:

- One patient (in the fulvestrant + anastrozole group) withdrew consent after randomisation before they received study treatment.
- Seventeen patients had missing tumour samples at baseline or surgery
    - including 1 patient who withdrew from the study due to an AE.
- Four patients were classified as protocol deviators (1 patient was found to be ER-ve; for 3 patients the time from study treatment to surgery was deemed by the investigator to be too long)
    - including 1 patient who withdrew from the study due to an AE.

Table 2 summarises the mean age of patients in the interim per protocol analysis reported in this synopsis.

Table 2 Age at baseline (per protocol patients [a])

	Fulvestrant	Fulvestrant + anastrozole	Anastrozole
n	35	29	35
Mean (SD) age, years	67.9 (8.5)	64.4 (10.5)	64.7 (8.7)

[a] Interim analysis on 30 July 2009.
N:Number of patients; SD:Standard deviation.

Efficacy

The efficacy data from an interim analysis of the efficacy data performed on 30 July 2009 are summarised in Table 3.

The analysis was per protocol except the Principal Investigator extended the acceptable time window for treatment to surgery 14 to 21 days to a wider range of 13 to 28 days. Following a review by the Principal Investigator, 4 patients were excluded from the per protocol analysis of efficacy: 1 patient was found to have violated an inclusion criterion (ER-ve at baseline); 3 patients underwent surgery more than 28 days after completing treatment.

Table 3 Summary of efficacy results (per protocol patients [a])

Endpoint		Fulvestrant	Fulvestrant + anastrozole	Anastrozole
ER index	n	35	29	35
	Pre-treatment H-score[b]	187.1	187.2	192.7
	% change from baseline (post-treatment)	-41%	-35%	-15%
Ki67 labelling index	n	35	29	35
	Pre-treatment geometric mean score (%)	21.8	24.7	22.0
	% change from baseline (post-treatment)	-81%	-85%	-89%
PgR index	n	29[c]	21[c]	29[c]
	Pre-treatment H-score[b]	164.6	165.4	172.8
	% change from baseline (post-treatment)	-37%	-44%	-42%

[a] Interim analysis on 30 July 2009.

[b] Tumour samples were assessed for ER/PgR staining. For each sample, tumour epithelial cells was categorised as ER/PgR negative (-/-); very weak (+/-); weak (+); moderate (++); or strong (+++). H-score = [(0.5 x %+/-) + (1 x %+) + (2 x %++) + (3 x %+++)].

[c] Patients with a score of 0 at baseline were omitted from the analysis (unlike ER status, PgR +ve status at baseline was not an inclusion criterion for the study).

ER:Oestrogen receptor; PgR:Progesterone receptor; n:Number of patients.

Safety

Overall, 69.2% of the 120 patients who received study treatment reported at least one AE (69.2% in the fulvestrant group, 66.7% in the fulvestrant + anastrozole group, 71.4% in the anastrozole group). In both the fulvestrant group and the anastrozole group, hot flush was the most commonly reported AE (17.9% and 19.0% of patients, respectively). In the fulvestrant + anastrozole group, headache and pain in extremity were the most commonly reported AEs (each reported by 10.3% of patients).

A total of 5 patients reported an SAE (3 in the fulvestrant + anastrozole group [atrial fibrillation, right mastectomy and procedural complication], 2 in the anastrozole group [subcutaneous abscess and pancytopenia]). None of the SAEs reported were considered by the investigator to be casually-related to study treatment. Two patients (both in the anastrozole group) withdrew from the study due to an AE (pancytopenia [an SAE] and cardiac arrhythmia [non-serious]).