Clinical Study Report Synopsis

Drug Substance	Fulvestrant
Study Code	D6997L00021
Edition Number	1
Date	20 August 2014

A Randomised, Double-Blind, Parallel-Group, Multicentre Study Comparing the Efficacy and Tolerability of Fulvestrant 500 mg versus Fulvestrant 250 mg in Postmenopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer Progressing or Relapsing after Previous Endocrine Therapy

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Study centre(s):

Total of 23 centres in mainland China.

Study dates		**Phase of development**
First patient enrolled	01 March 2011	III
Last patient completed	25 March 2014	

Publications

No publication when clinical study report (CSR) was developed.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			**Outcome Variable**
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To compare the efficacy of fulvestrant 500 mg treatment with fulvestrant 250 mg treatment in terms of PFS.	PFS
Secondary	PK	To describe the PK profile of fulvestrant 500 mg and fulvestrant 250 mg.	CL/F, Vss/F, C_{max}, t_{max}, C_{min}, $AUC_{0-\tau}$ and $t_{1/2}$
Secondary	Efficacy	To compare the ORR of patients treated with fulvestrant 500 mg with the ORR of patients treated with fulvestrant 250 mg.	ORR=CR + PR, defined by RECIST 1.1 criteria
Secondary	Efficacy	To compare CBR of patients treated with fulvestrant 500 mg with the CBR of patients treated with fulvestrant 250 mg.	CBR=CR + PR + SD ≥24 weeks defined by RECIST 1.1 criteria
Secondary	Efficacy	To estimate the DoR of patients treated with fulvestrant 500 mg and fulvestrant 250 mg.	DoR

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	To estimate the DoCB of patients treated with fulvestrant 500 mg and fulvestrant 250 mg.	DoCB
Secondary	Safety	To assess the tolerability of fulvestrant 500 mg treatment compared with fulvestrant 250 mg treatment.	Frequency and severity of adverse events

$AUC_{0-\tau}$=area under the plasma concentration-time curve from the time of dosing to the end of the dosing interval; CBR=clinical benefit rate; CL/F=apparent clearance; C_{max}=maximum plasma concentration of drug in a standard dosing interval; C_{min}=minimum plasma concentration of drug in a standard dosing interval; CR=complete response; DoCB=duration of clinical benefit; DoR=duration of response; ORR=objective response rate; PFS=progression-free survival; PK=pharmacokinetic; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours; SD=stable disease; $t_{½}$=terminal plasma half-life; t_{max}=time to $C_{max;}$ Vss/F=apparent volume of distribution.
Note: For PK parameters, only the PK parameters that could be derived directly from the plasma concentration-time data were summarised and reported in Section 5.2.2 (eg, the C_{min} parameter). All other appropriate PK parameters were determined using population PK modelling techniques and are reported separately from the clinical study report.

Study design

This was a randomised, double-blind, parallel-group, multicentre, phase III study to compare the efficacy and tolerability of fulvestrant 500 mg versus fulvestrant 250 mg in postmenopausal women with oestrogen receptor (ER) positive advanced breast cancer progressing or relapsing after previous endocrine therapy. A total of 221 postmenopausal patients were randomised in the study from 23 centres in mainland China. Eligible patients were randomised in a 1:1 ratio to receive fulvestrant 500 mg or fulvestrant 250 mg. Treatment would continue until disease progression, unless any of the criteria for treatment discontinuation were met first.

The first 30 patients in each group who consented to the pharmacokinetic (PK) measurements would have PK plasma samples taken.

Target subjects population and sample size

Postmenopausal women with ER positive advanced breast cancer who had progressed or relapsed on endocrine therapy which could be either an antioestrogen (AO) or an aromatase inhibitor (AI).

The ratio of post-AO and post-AI patients was monitored during study recruitment and for consistency with the CONFIRM (COmparisoN of Faslodex In Recurrent or Metastatic breast cancer) study (42.5% post-AI, sponsored by AstraZeneca), enrolment of post-AI patients was stopped once 100 post-AI patients (45%) had been randomised.

Inclusion/exclusion criteria

Key inclusion criteria

For inclusion into the study, patients were required to fulfil the following key criteria:

1. Postmenopausal woman, defined as a woman fulfilling any of the following criteria:

   - Having undergone a bilateral oophorectomy
   - Age ≥60 years.
   - Age <60 years and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle stimulating hormone (FSH) and oestradiol level in the postmenopausal range (utilising ranges from the local laboratory facility).
   - If taking tamoxifen or toremifene, and age <60 years, then FSH and plasma oestradiol level in the postmenopausal ranges (utilising ranges from the local laboratory facility).

2. Histological/cytological confirmation of breast cancer

3. Documented positive ER status of primary or metastatic tumour tissue, according to the local laboratory parameters.

4. Requiring hormonal treatment:

(a) Relapsing during, or within 12 months of completion of, adjuvant endocrine therapy (tamoxifen, toremifene or AIs such as anastrozole, letrozole and exemestane), or

(b) Progressing on an endocrine therapy (tamoxifen, toremifene or AIs such as anastrozole, letrozole and exemestane) provided that this endocrine treatment was started at least 12 months after the completion of adjuvant endocrine treatment, or

(c) Progressing on an endocrine therapy (tamoxifen, toremifene or AIs such as anastrozole, letrozole and exemestane) given as first treatment for patients with *de novo* advanced breast cancer

5. Patients fulfilling one of the following criteria:

   - Patients with measurable disease as per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria.
   - Patients with bone lesions, lytic or mixed (lytic + sclerotic), in the absence of measurable disease as defined by RECIST 1.1 criteria.

6. World Health Organisation performance status 0, 1 or 2.

For inclusion in the PK research component of the study, patients were required to fulfil the following criteria:

- Provision of informed consent for PK research component.

Key exclusion criteria

Any of the following was regarded as a key criterion for exclusion from the study:

1. Presence of life-threatening metastatic visceral disease, defined as extensive hepatic involvement, or any degree of brain or leptomeningeal involvement (past or present), or symptomatic pulmonary lymphangitic spread. Patients with discrete pulmonary parenchymal metastases were eligible, provided their respiratory function was not compromised as a result of disease.

2. More than one regimen of chemotherapy for advanced disease.

3. More than one regimen of endocrine therapy for advanced disease.

4. Extensive radiation therapy within the last 4 weeks (greater than or equal to 30% marrow or whole pelvis or spine) or cytotoxic treatment within the past 4 weeks prior to screening laboratory assessment, or strontium-90 (or other radiopharmaceuticals) within the past 3 months.

5. Treatment with a non-approved or experimental drug within 4 weeks before randomisation.

6. Any of the following laboratory values:

    - Platelets $<100 \times 10^9$/L
    - Total bilirubin $>1.5 \times$ Upper Limit of Reference Range (ULRR)
    - Alanine aminotransferase or aspartate aminotransferase $>2.5 \times$ ULRR if no demonstrable liver metastases or $>5 \times$ ULRR in presence of liver metastases
    - Severe renal impairment (creatinine clearance <30 mL/min).

Investigational product & Comparator(s): dosage, mode of administration and batch numbers

Fulvestrant 500 mg was given as two 5 mL intramuscular (im) injections (2 fulvestrant injections), one in each buttock, on Days 1, 15, 29 and every 28 days (±3 days) thereafter.

Fulvestrant 250 mg was given as two 5 mL im injections (1 fulvestrant injection + 1 placebo injection), one in each buttock, on Days 1, 15 (2 placebo injections only), 29 and every 28 days (±3 days) thereafter.

After the database lock for the primary analysis, patients had their treatment unblinded and remained in the study, and transferred to open label study drug supplies until they ceased to receive clinical benefit from the study treatment.

After study treatment was unblinded, patients who remained on fulvestrant 250 mg received only one 5 mL dose of fulvestrant 250 mg im injection, as the placebo injection previously required to preserve the double blind nature of the study was no longer needed.

Batch numbers

Fulvestrant 250 mg: GJ625, HK907 and KC955/1.

Placebo for fulvestrant 250 mg: GY878.

Duration of treatment

Treatment continued until disease progression, unless any of the criteria for treatment discontinuation were met first.

Statistical methods

The primary analysis for Progression-Free Survival (PFS) was planned to be conducted when at least 150 progression events had been confirmed and all patients had the opportunity for a post-baseline RECIST assessment. Data cut-off (DCO) for the analysis occurred on 25 March 2014, at which time 152 progression events had been recorded.

Prior to the analysis of this study it was decided that the results of this study would be considered to be consistent with that of the CONFIRM study if the hazard ratio (HR) point estimate for the treatment comparison was <1 (ie, if it was in the same direction as in CONFIRM). With a sample size of 220 randomised patients and 150 progression events, if treatment effect is consistent between ethnicities/the study populations, there is an 89% chance the HR would be <1. As this study was designed to assess the HR, it was not formally powered to detect a statistically significant difference between two treatment groups.

The analysis of the primary efficacy variable, PFS, was performed for the Full Analysis Set (FAS) using a log-rank test stratified by last endocrine therapy received prior to fulvestrant (AO vs. AI). In addition, secondary analyses for the primary variable of PFS were carried out on the ‘Per Protocol Set’ (PPS). Supporting analysis was performed using the Cox proportional hazard model to investigate any impact of baseline covariates.

The objective response rate (ORR) and clinical benefit rate (CBR) were analysed using a logistic regression model with treatment factor and last endocrine therapy received prior to fulvestrant (AO vs. AI). Duration of response (DoR) and duration of clinical benefit (DoCB) were summarised using the Kaplan-Meier method. No interim analysis was carried out in this study. Summaries of safety variables were presented by study treatment actually received.

For the PK part, no specific statistical hypothesis was tested. The intention was to collect PK samples from the first 30 patients in each treatment group consenting to samples being taken.

As the study was double blind it wasn't possible to distinguish to which group each of these patients belonged to prior to unblinding. Therefore the actual treatment group totals were not able to reflect the equal split of patients in each treatment group as originally intended. The analysis took place when the full PK data were available and the whole study database had been locked.

Only the PK parameters that could be derived directly from the plasma concentration-time data are summarised and reported in Section 5.2.2 (eg, the minimum plasma concentration of drug in a standard dosing interval [C_{min}] parameter). All other appropriate PK parameters were determined using population PK modelling techniques and are reported separately from the CSR.

Results

Subject population

- Altogether 221 patients were randomised 1:1 between fulvestrant 500 mg and fulvestrant 250 mg; 219 patients received the study treatment and there were 152 progression events (maturity 69% [152/221]) at the time of DCO.

- Key demographic and baseline characteristics were balanced between the treatment groups.

Summary of efficacy results

- The study met the pre-defined success criterion (HR<1) for the PFS in the FAS, HR=0.75 [95% CI: 0.54, 1.03] (p=0.078, although the study was not powered for statistical significance) favouring the fulvestrant 500 mg group as compared to those treated with fulvestrant 250 mg group, with median PFS 8.0 months vs. 4.0 months, corresponding to a 25% reduction in risk of disease progression.

  - The HR for the PFS in the FAS is consistent with the observed HR in the CONFIRM study (HR=0.80 [95% CI: 0.68, 0.94], p=0.006, Section 1.2).

  - Results from the subgroup analyses were consistent across all subgroups by favouring the fulvestrant 500 mg group in terms of the point estimate of the HR (<1).

  - For PFS, HRs <1 were also achieved within the pre-defined subgroups of last endocrine therapy received prior to fulvestrant (AO vs. AI), HR=0.86 [95% CI: 0.54, 1.37] and HR=0.65 [95% CI: 0.42, 1.03], for post-AO and post-AI respectively. The maturity in these subgroups was 59% (post-AO subgroup) and 81% (post-AI subgroup) respectively, reflecting the later accrual of patients to the post AO subgroup. The median PFS in post-AO subgroup was 8.1 months vs. 5.6 months respectively; and in post-AI subgroup was 5.8 months vs. 2.9 months in fulvestrant 500 mg and fulvestrant 250 mg groups respectively.

  - For PFS, HRs in the post-AO or post-AI subgroups appeared numerically different to the CONFIRM study (HR=0.76 [95% CI: 0.62, 0.94] and HR=0.85 [95% CI: 0.67, 1.08], for post-AO and post-AI respectively, Di Leo et al 2009). It is likely this difference can be attributed to the lower patient numbers and wide confidence intervals for the subgroups in the current study, together with the lower maturity in the post-AO subgroup.

- The following secondary endpoints all favoured patients receiving fulvestrant 500 mg over fulvestrant 250 mg:

  - ORR odds ratio=1.44 [95% CI: 0.93, 2.24]*, ORR 28% vs. 17% (*p=0.107, although the study was not powered for statistical significance)

  - CBR odds ratio=1.37 [95% CI: 1.04,1.80]*, CBR 48% vs. 33% (*p=0.023, although the study was not powered for statistical significance)

  - DoCB median 14.3 months vs. 13.8 months

- The following secondary endpoint did not favour fulvestrant 500 mg over fulvestrant 250 mg:

  - DOR median 16.6 months vs. 22.2 months with a small sample size of responders (number of responders 16 vs. 11)

- Efficacy results consistently favouring fulvestrant 500 mg were seen in this study, and are consistent with the outcome of the Phase III CONFIRM study that confirmed superior efficacy for fulvestrant 500 mg.

Summary of pharmacokinetic results

- Steady-state plasma concentrations for the 500 mg treatment group in this study population were achieved earlier and were higher than those for the 250 mg treatment group.

Summary of safety results

- The safety profile of fulvestrant 500 mg and 250 mg were broadly similar, and consistent with the known safety profile of fulvestrant.

Date of report

20 August 2014