Final OS Analysis Abbreviated Clinical Study Report	
Drug Substance	Fulvestrant
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A Randomised, Double-blind, Parallel-group, Multicentre, Phase III Study to Compare the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Anastrozole (ARIMIDEX™) 1 mg as Hormonal Treatment for Postmenopausal Women with Hormone Receptor-Positive Locally Advanced or Metastatic Breast Cancer Who Have Not Previously Been Treated with Any Hormonal Therapy (FALCON)

Study dates: First patient enrolled: 17 October 2012
Last patient last visit: 11 July 2022
The analyses presented in this report are based on a Final analysis clinical data cut-off (DCO) date of 11 July 2022; Primary analysis results were previously presented in the main CSR dated 05 August 2016 (DCO: 11 April 2016).

Phase of development: Therapeutic confirmatory (III)

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

Study centre(s)

The study was performed at 175 centres in 20 countries: Argentina, Brazil, Canada, China, Czech Republic, Italy, Japan, Mexico, Peru, Poland, Romania, Russia, Slovakia, South Africa, Spain, Taiwan, Turkey, Ukraine, United Kingdom, and United States (US).

Publications

- Robertson JFR et al, Lancet 388 (2016) 2997–3005
- Robertson JFR et al, European Journal of Cancer 94 (2018) 206-215
- Noguchi S et al, Breast Cancer 25(3) (2018)356-364.

Objectives and criteria for evaluation

For the complete objectives and endpoints analysed and reported during the primary analysis, refer to the main Clinical Study Report (CSR) (05 August 2016).

In the survival follow-up phase of this study (after the primary analysis), the data for the following secondary objectives were collected, analysed and reported in this final analysis report, as described in the CSP:

- To compare the overall survival (OS) of patients treated with fulvestrant 500 mg versus patients treated with anastrozole 1 mg.
- To compare the quality of life (QoL) of patients treated with fulvestrant 500 mg versus patients treated with anastrozole 1 mg.
- To compare the safety and tolerability (serious adverse events [SAEs] only) of fulvestrant 500 mg treatment versus that of anastrozole 1 mg treatment.

Study design

This was a randomised, double-blind, double-dummy, international, multicentre study comparing the efficacy and tolerability of fulvestrant (500 mg) with anastrozole (1 mg) in postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer (confirmed by histology), who had not previously been treated with any hormonal therapy.

The primary analysis was performed when 309 progression events had occurred (see main CSR [05 August 2016]). After the DCO for the primary analysis (11 April 2016), all remaining patients, regardless of whether they were still receiving randomised treatment, entered the survival follow-up phase.

Further collection of data on objective disease progression stopped after the DCO for the primary analysis (ie, 12-weekly CT/MRI scans were to no longer be recorded on the eCRF). In the survival follow-up phase, study visits were conducted in order to complete health-related quality of life (HRQoL) assessments (at 3-monthly intervals prior to objective disease progression, at the treatment discontinuation visit, at 3-months post-progression, and

thereafter at 6-monthly intervals post-progression until the DCO for the OS analysis), administer/dispense study medication (for patients still receiving randomised treatment), and to determine survival status. The only safety data collected for patients during the survival follow up phase on the study were SAEs and deaths. During the survival phase of the study, patients were otherwise managed according to standard clinical practice.

Patients who entered the survival follow-up phase while still receiving randomised treatment could continue to receive treatment for as long as they received clinical benefit (until criteria for discontinuation were met). Following confirmation of objective disease progression per standard-of-care assessment, follow-up could be conducted by telephone, and HRQoL questionnaires could be posted to patients for completion, if appropriate.

A survival analysis was performed at the same time as the primary analysis and again when at least 65% of patients had died and at least 8 years had passed since the last patient was enrolled. After this point, data collection was to cease for this study, the study database was to be closed, and the patient's treatment was to be unblinded.

Patients will be permitted to continue to receive open-label study treatment beyond the closure of the database for OS (11 July 2022) if, in the opinion of the Investigator, they continue to receive benefit from treatment with fulvestrant or anastrozole and cannot access appropriate treatment outside of the study. Placebo treatment was discontinued once analysis of OS results was completed.

Target subject population and sample size

See the main CSR (05 August 2016) for detailed information regarding the study eligibility criteria and sample size.

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

The investigational products provided in this study (manufactured by AstraZeneca) were as follows: fulvestrant (2 × 250 mg/5 mL solution for intramuscular injection; 500 mg fulvestrant); placebo to match fulvestrant (2 × 5 mL solution for intramuscular injection, 0 mg fulvestrant); anastrozole (tablet, 1 mg anastrozole); and placebo to match anastrozole (tablet, 0 mg anastrozole). To maintain the double-blind, double-dummy design of the trial, each patient received both study treatments, 1 of which was placebo.

Duration of treatment

Treatment with study medication was to continue until objective disease progression, unless any of the criteria for treatment discontinuation were met first.

Statistical methods

See main CSR (05 August 2016).

Subject population

A total of 462 patients were randomised in a 1:1 ratio to receive either fulvestrant 500 mg or anastrozole 1 mg; of the 462 randomised patients, 460 patients (228 [99.1%] patients in the fulvestrant arm and 232 [100%] patients in the anastrozole arm) received study treatment.

At the time of OS DCO (11 July 2022), 25 (10.9%) patients in the fulvestrant arm and 31 (13.4%) patients in the anastrozole arm were ongoing in the blinded study, and 12 (5.3%) patients in the fulvestrant arm and 10 (4.3%) patients in the anastrozole arm were continuing to receive study treatment. Treatment had been discontinued prior to the OS DCO in 216 (94.7%) patients in the fulvestrant arm and 222 (95.7%) patients in the anastrozole arm.

Summary of efficacy results

- At the time of the final OS analysis, 314 death events had occurred (fulvestrant arm: 157 [68.3%] patients; anastrozole arm: 157 [67.7%] patients). There was no statistically significant difference in OS between the treatment arms (hazard ratio [HR]: 0.966; 95% CI: 0.773, 1.206; 2-sided p = 0.7579).
- Overall survival analyses by subgroups were generally consistent with the overall population, although some numbers were too small to allow for meaningful comparisons.
- In patients with non-visceral disease, a 15% reduction in the risk of death (HR: 0.846; 95% CI: 0.599, 1.195) was observed with fulvestrant (median OS: 65.2 months) vs anastrozole (median OS: 47.8 months).
- There was no statistically significant difference in time to deterioration in the FACT-B total score or TOI score between the fulvestrant and anastrozole treatment arms.

Summary of safety results

The key exposure, and safety findings from this study were:

- At the final DCO for OS (11 July 2022), the median actual treatment duration was 14.7 months (range: 0.9 to 111.3 months) in the fulvestrant arm, and 13.9 months (range: 0.2 to 110.5 months) in the anastrozole arm.
- Deaths were reported in 316 (68.7%) patients in the safety analysis set. The majority of deaths in both treatment arms were due to disease under investigation only (139 [61.0%] patients in the fulvestrant arm and 132 [56.9%] patients in the anastrozole arm).
- Adverse events with an outcome of death were reported for 16 (3.5%) patients, with 7 (3.1%) patients in the fulvestrant arm, and 9 (3.9%) patients in the anastrozole arm. No AEs with an outcome of death were causally related to study treatment.
- Serious AEs, regardless of causality, were reported for a similar proportion of patients treated with fulvestrant (39 [17.1%] patients) and anastrozole (36 [15.5%] patients). Five (2.2%) patients in the fulvestrant arm and 3 (1.3%) patients in the anastrozole arm reported SAEs which were causally related to study treatment.

- Serious AEs that led to discontinuation of study treatment were reported in similar proportions of patients in the fulvestrant (15 [6.6%] patients) and anastrozole (11 [4.7%] patients) arms. Only 2 (0.9%) patients in the fulvestrant and one (0.4%) patient in the anastrozole arm had reported causally related SAE that led to discontinuation of the study treatment.
- Overall, the safety findings remained consistent with the known safety profile of fulvestrant and anastrozole. No new safety findings were identified.

Conclusion(s)

- Median OS was similar between the fulvestrant arm (44.8 months) and the anastrozole arm (42.7 months). There was no statistically significant difference in OS between the treatment arms.
- The positive trend observed in OS for fulvestrant in non-visceral disease was consistent with the primary analysis.
- There were no meaningful differences in QoL outcomes between the fulvestrant and anastrozole treatment arms.
- Overall, safety findings remained consistent with the known safety profile of fulvestrant and anastrozole. No new safety findings were identified.