Clinical Study Report Synopsis	
Drug Substance	AZD9833 (camizestrant)
Study Code	D8530C00002
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SERENA-2: A Randomised, Open-Label, Parallel-Group, Multicentre Phase 2 Study Comparing the Efficacy and Safety of Oral AZD9833 versus Fulvestrant in Women with Advanced ER-Positive HER2-Negative Breast Cancer

Study dates: First participant enrolled: 22 April 2020
Last participant last visit for primary analysis: 30 August 2022
The primary analyses presented in this report are based on a clinical data cut-off date of 30 August 2022

Phase of development: Therapeutic exploratory (II)

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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

Study Centres

The study was conducted at 82 sites in 16 countries.

Publications

Oliveira M, Bennett M, Carroll D, Khalil Ali, Mather R, Maudsley R et al. SERENA-2: A Randomised, Open-Label, Parallel-Group, Multicentre Phase 2 Study Comparing the Efficacy and Safety of Oral AZD9833 versus Fulvestrant in Women with Advanced ER+ HER2- Breast Cancer. Cancer Res2021;81(4_Supplement):OT-09-02.

Oliveira M, Pominchuk D, Nowecki Z, Hamilton E, Kulyaba Y, Andabekov T et al. Camizestrant, a next-generation oral SERD vs fulvestrant in post-menopausal women with advanced ER-positive HER2-negative breast cancer: Results of the randomized, multi-dose Phase 2 SERENA-2 trial. Cancer Res2023;83(5_Supplement):GS3-02.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints/Variables
Primary	
To determine the clinical efficacy (as assessed by PFS) of AZD9833 (camizestrant) when compared to fulvestrant in women with advanced ER-positive HER2-negative breast cancer	PFS assessed by the Investigator as defined by RECIST version 1.1
Secondary	
To determine anti-tumour effect of camizestrant when compared to fulvestrant in women with advanced ER-positive HER2-negative breast cancer	Based on tumour response assessed by the Investigator, as defined by RECIST version 1.1: • ORR • DoR • Best percentage change in tumour size and percentage change in tumour size at 16 weeks
To determine the effect of camizestrant on survival and clinical benefit when compared to fulvestrant in women with advanced ER-positive HER2-negative breast cancer	• OS • CBR_{24}
To evaluate the PK of camizestrant in this patient population at steady state	Plasma concentrations of camizestrant and, if appropriate, metabolite(s) on Day 15 (pre- and post-dose) and Day 29 (pre-dose)
To evaluate the pharmacodynamics of camizestrant and fulvestrant in a subgroup of patients with advanced ER-positive HER2-negative breast cancer	• Percent change from baseline in ER and PgR expression assessed by the manual H-score method • Percent change from baseline in Ki67 labelling index
To evaluate the effect of camizestrant and fulvestrant on the patients' HRQoL, as assessed by patient-completed HRQoL questionnaires	Changes from baseline in total/subscale scores of the EORTC QLQ-C30, EORTC QLQ-BR23, NEI VFQ-25, and EQ-5D-5L
Safety	
To evaluate the safety and tolerability of camizestrant when compared to fulvestrant in women with advanced ER-positive HER2-negative breast cancer	• AEs/SAEs • Vital signs, ECGs, clinical chemistry, haematology, urinalysis parameters

Exploratory objectives and endpoints are included in the CSR body. All exploratory endpoints except for CCI [redacted] will be reported outside of the CSR.

AE = adverse event; CBR_{24} = clinical benefit rate at 24 weeks; CSR = clinical study report; DoR = duration of response; ECG = electrocardiogram; EORTC = European Organisation for Research and Treatment of Cancer; EORTC QLQ-BR23 = EORTC quality of life questionnaire – breast cancer module; EORTC QLQ-C30 = EORTC quality of life questionnaire – core questionnaire = ER = estrogen receptor; EQ-5D-5L = EuroQol 5 Dimension 5 level; HER2 = human epidermal growth factor receptor 2; HRQoL = health-related quality of life; NEI VFQ-25 = National Eye Institute 25-Item Visual Function Questionnaire; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; CCI [redacted]; PgR = progesterone receptor; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = serious adverse event.

Study Design

This was a randomised, open-label, parallel-group, multicentre Phase 2 study to compare the efficacy and safety of daily per oral (PO) camizestrant at 3 doses (75 mg, 150 mg, and 300 mg) versus intramuscular fulvestrant in women with advanced estrogen receptor (ER)-positive human epidermal growth factor receptor 2 (HER2)-negative breast cancer. Post-menopausal women with histologically or cytologically confirmed metastatic or loco-regionally recurrent disease before randomisation and fulfilling all of the inclusion criteria and none of the exclusion criteria were included. Randomisation was stratified according to the prior use of cyclin-dependent kinase (CDK)4/6 inhibitors and the presence of liver and/or lung metastases.

Target Population and Sample Size

The study enrolled post-menopausal female patients aged at least 18 years with an ER-positive, HER2-negative, metastatic, or loco-regionally recurrent adenocarcinoma of the breast suitable for treatment with fulvestrant.

A sample size of approximately 288 patients, randomised in equal proportions to the 4 treatment groups was estimated to be required to observe a total of at least 108 progression-free survival (PFS) events for each pairwise comparison against fulvestrant. As of December 2020, and the decision to stop enrolment to the camizestrant 300 mg arm, the resulting total sample size across the 3 enrolling treatment arms was estimated to be approximately 216, with approximately an additional 20 patients from the camizestrant 300 mg arm enrolled up to recruitment closure of this arm. The primary analysis could only be triggered when a minimum of 108 events was observed for the pairwise comparison of 75 mg and 150 mg camizestrant doses versus fulvestrant.

A hazard ratio (HR) of 0.59 for each pairwise treatment comparison versus fulvestrant was considered of interest. Under the assumption that a 5-month median PFS would be observed on fulvestrant, this would be equivalent to a 3.5-month increase in median PFS over fulvestrant. A minimum of 108 events for the pairwise comparison of each camizestrant dose

of interest versus fulvestrant would provide 86% power at the 2-sided 10% significance level if the assumed true treatment effect was HR = 0.59.

Investigational Product and Comparator: Dosage, Mode of Administration and Batch Numbers

Patients were randomly assigned in a 1:1:1:1 ratio to receive one of the following 4 treatments, consisting in 4-week treatment cycles until disease progression (assessed by the Investigator as defined by Response Evaluation Criteria in Solid Tumours version 1.1):

- Camizestrant (75 mg, orally, once daily)
- Camizestrant (150 mg, orally, once daily)
- Camizestrant (300 mg, orally, once daily)
- Fulvestrant (500 mg intramuscular, Day 1, Day 15, Day 29, and 4-weekly thereafter)

Twelve batches of camizestrant were used in this study. Individual batch numbers and further information are included in the clinical study report.

Duration of Treatment

There was no maximum duration of treatment, and patients could continue to receive study treatment as long as they continued to show clinical benefit, as judged by the Investigator.

Statistical Methods

All efficacy analyses were performed on the full analysis set (FAS). The primary analysis, which was a formal comparison of camizestrant to fulvestrant, only applied to camizestrant 75 mg and 150 mg treatment arms. Results of all statistical analyses were presented using 90% confidence intervals (CIs) and 2-sided p-values. The treatment comparison of interest was each dose level of camizestrant versus fulvestrant. Data accrued from the camizestrant 300 mg treatment arm was summarised and reported as appropriate.

All safety analyses were performed on the safety analysis set. Safety data were presented using descriptive statistics. Safety and tolerability were assessed in terms of adverse events (AEs) (including serious adverse events [SAEs]), deaths, laboratory data, vital signs, and electrocardiograms (ECGs). These were collected for all patients.

For the primary analysis, the null hypothesis tested was that there was no treatment effect, (ie, there was no difference in PFS between patients treated with any dose of camizestrant and patients treated with fulvestrant).

- H_0: PFS HR $_{AZD9833/fulvestrant}=1$
- H_1: PFS HR $_{AZD9833/fulvestrant}\neq 1$

Each dose of camizestrant of interest was compared with fulvestrant in a pairwise comparison.

A sensitivity analysis for the primary endpoint of this study was based on the blinded independent central review (BICR) of the radiological scans.

As this was a Phase 2 study, no adjustments for multiplicity were made.

The PFS was analysed based on the FAS using a stratified Cox Proportional-Hazards model, allowing for the effect of study treatment and adjusting for the stratification factors: prior use of CDK4/6 inhibitors (yes/no) and presence of liver and/or lung metastases (yes/no). A stratified log-rank test adjusting for prior use of CDK4/6 inhibitors and presence of liver and/or lung metastases was used to compare each camizestrant dose against fulvestrant.

For each patient, the BICR defined the overall visit response (ie, the response obtained overall at each visit by assessing target lesions, non-target lesions, and new lesions) data and no programmatic derivation of visit response was necessary. Progression-free survival was derived programmatically from the overall visit responses determined for each visit.

The objective response rate (ORR) and clinical benefit rate at 24 weeks (CBR_{24}) were compared between camizestrant (each dose level) and fulvestrant using a logistic regression model adjusting for prior use of CDK4/6 inhibitors and presence of liver and/or lung metastases.

The absolute value of the change in tumour size from baseline, and the percentage change in tumour size from baseline were summarised using descriptive statistics and presented at each timepoint and by randomised treatment group. The change from baseline in tumour size at 16 weeks and best change from baseline in tumour size were also summarised and presented by randomised treatment group.

The OS data were analysed at the time of the primary analysis of PFS using the same methodology and model as PFS analyses. Further survival analyses could be conducted after CCI and CCI of patients had died.

Study Population

In total, 302 patients were enrolled, and 240 patients were randomised and received treatment; 62 patients were not randomised, of which 59 patients were screen failures, 2 were withdrawals by patients, and 1 patient was unassigned due to closed enrolment. Of the 240 patients assigned to treatment, 74 patients were assigned to camizestrant 75 mg, 73 patients were assigned to camizestrant 150 mg, 20 patients were assigned to camizestrant 300 mg, and 73 patients were assigned to fulvestrant. At the time of the data cut-off (DCO) (30 August 2022), 194 (80.8%) patients had discontinued treatment, of which 4 (1.7%) patients had discontinued due to AEs. The study population was representative of the intended target population of women with ER-positive and HER2-negative advanced breast cancer. The age distribution was as expected and well balanced across treatment arms.

Summary of Efficacy Results

- In the overall population, in the analysis of the primary endpoint, camizestrant produced a statistically significant and clinically meaningful improvement in PFS over fulvestrant at both 75 mg (HR [90%CI]: 0.59 [0.42 – 0.82]; p-value = 0.0167) and 150 mg (HR [90% CI]: 0.64 [0.46 – 0.89]; p-value = 0.0090) camizestrant doses.
- The BICR sensitivity analysis showed a statistically significant benefit in PFS at both 75 mg (p-value = 0.0065) and 150 mg (p-value=0.0006) doses of camizestrant over fulvestrant, consistent with the Investigator assessment.
- In the subgroups of patients with prior use of CDK4/6i, with liver and/or lung metastases, with detectable estrogen receptor 1 mutation (*ESR1*m) at baseline, and sensitive to endocrine therapy, camizestrant 75 mg and camizestrant 150 mg produced a clinically meaningful improvement in PFS over fulvestrant.
- Camizestrant 75 mg and camizestrant 150 mg increased ORR when compared to fulvestrant.
- Camizestrant at 75 mg and at 150 mg increased clinical benefit rate at 24 weeks when compared to fulvestrant.
- At DCO, the overall survival (OS) maturity was 27.1% across all treatment arms and 26.4% excluding the camizestrant 300 mg treatment arm. Overall survival data were too immature for any interpretations to be made.
- Health-related quality of life results indicated no long-term deterioration in any treatment arm during treatment.

Summary of Pharmacokinetic Results

Plasma concentrations of camizestrant showed an increasing exposure with dose.

Summary of Pharmacodynamic Results

Only 1 patient was included in the pharmacodynamic analysis set; therefore, statistical analysis was not performed.

Summary of Safety Results

- Camizestrant 75 mg and camizestrant 150 mg were well tolerated.
- No new safety signals were identified.
- A greater number of AEs and dose interruptions were observed in the camizestrant 150 mg treatment arm when compared to camizestrant 75 mg treatment arm.
- Treatment-related dose interruptions were infrequent and of short duration.
- Overall, SAEs occurrence was infrequent and comparable across the treatment arms, SAE reporting does not indicate an increase in SAE rate for camizestrant when compared to fulvestrant, and no dose-relationship has been observed.
- Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher treatment-related AEs, SAEs, dose reductions, and discontinuations were infrequent.
- There was a dose-dependent CCI [redacted] AE profile for camizestrant.

- One (1.4%) patient in the camizestrant 150 mg treatment arm experienced an AE (COVID-19 pneumonia) with an outcome of death, which was assessed as not treatment-related to treatment.
- There were no trends observed in haematology, clinical chemistry, or urinalysis variables for camizestrant or fulvestrant.
- Camizestrant produced a dose-dependent reduction in resting heart rate, which was apparent at Cycle 1 Day 8 and appeared to plateau at later time points. The 28-day follow-up visit indicated that for camizestrant 75 mg and camizestrant 150 mg, there was recovery in heart rate, which returned to levels comparable to screening.

Conclusions

- The study met its primary objectives: camizestrant at both 75 mg and 150 mg doses improves PFS when compared to fulvestrant.
- Camizestrant delivers statistically significant and clinically meaningful PFS benefit at both 75 mg and 150 mg doses when compared to fulvestrant in this advanced breast cancer monotherapy study.
- Both camizestrant 75 mg and 150 mg doses were well tolerated; Grade 3 or higher TRAEs, SAEs, dose reductions and discontinuations were infrequent.
- A greater number of AEs and dose interruptions was observed at camizestrant 150 mg when compared to camizestrant 75 mg. Treatment-related dose interruptions were also infrequent and of short duration.
- No new safety signals were identified in this study.
- The results of the SERENA-2 study support further development of camizestrant in ER-positive HER2-negative breast cancer.