Clinical Study Report Synopsis	
Drug Substance	AZD9833 (INN: camizestrant)
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A Randomised, Open-Label, Parallel-Group, Presurgical Study to Investigate the Biological Effects of AZD9833 in Women with ER-positive, HER2-negative Primary Breast Cancer (SERENA-3)

Study dates: First patient enrolled: 02 November 2020
Last patient last visit: 19 June 2023
The analyses presented in this report are based on a clinical data lock date of 07 August 2023

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 centre(s)

The study was conducted at 13 sites in 3 countries.

Publications

Robertson J, et al. SERENA-3: A randomized pre-surgical window of opportunity study assessing dose and duration of camizestrant treatment in post-menopausal women with ER-positive, HER2-negative primary breast cancer. San Antonio Breast Cancer Symposium 2023;RF01-01.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints/Variables
Primary	
• To explore the ER PD effects of AZD9833 (camizestrant) between pre- and on-treatment tumour samples in women with early breast cancer after 5 to 7 days and 12 to 15 days of camizestrant treatment.	• Change from baseline in ER expression between pre- and on-treatment tumour samples measured by IHC and assessed by the manual H-score method.
Secondary	
• To explore the PgR and Ki67 PD effects of camizestrant between pre- and on-treatment tumour samples in women with early breast cancer after 5 to 7 and 12 to 15 days of camizestrant.	• Change from baseline in PgR expression between pre- and on-treatment tumour samples measured by IHC and assessed by the manual H-score method. • Change from baseline in Ki67 labelling index between pre- and on-treatment tumour samples measured by IHC.
• To evaluate the safety and tolerability of camizestrant in this patient population.	• AEs/SAEs. • Vital signs, ECGs.
• To evaluate the PK of camizestrant in this patient population.	• Plasma concentrations of camizestrant on the biopsy day.

Exploratory objectives and endpoints are included in the Clinical Study Report (CSR) body. All exploratory endpoints will be reported outside of the CSR.

AE = adverse event; ECG = electrocardiogram; ER = oestrogen receptor; IHC = immunohistochemistry; Ki67 = antigen Ki67; PD = pharmacodynamics; PgR = progesterone receptor; PK = pharmacokinetics; SAE = serious adverse event.

Study design

This was a three-stage, randomised, open-label, parallel-group, multicentre study to investigate the biological effects of different doses and durations of daily camizestrant in post-menopausal women with primary breast cancer. Patients newly diagnosed with histologically oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative invasive breast cancer involving a palpable tumour of any size, or a tumour

with an ultrasound of ≥ 1.0 cm and fulfilling all the inclusion criteria and none of the exclusion criteria were included. Stage 1, Stage 2, and Stage 3 comprised 2, 3, and 2 treatment groups to which post-menopausal patients were randomised, respectively.

Stage 1

After the screening visit (up to 21 days prior to randomisation) and confirmation of eligibility, patients were randomly assigned in a 1:1 ratio to receive one of the following 2 treatments:

- Camizestrant (75 mg, for 5 to 7 days)
- Camizestrant (150 mg, for 5 to 7 days)

During the treatment period, patients attended study visits on: Day 1, day of biopsy (Day 5, 6, or 7), and day of surgery (following a washout from camizestrant for at least 5 days). In the event that a patient was undergoing longer-term neoadjuvant therapy rather than surgery, the 'surgery day' visit was to be conducted on Day 13 (+ 3 days). A treatment window of 5 to 7 days, along with a washout period of 5 days was considered to permit curative intent surgery within existing standard of care timeframes. Throughout the study, patients were asked to report adverse events (AEs) and the use of concomitant medications. Safety assessments (physical examination, vital signs, electrocardiograms (ECGs), clinical safety laboratory assessments) were performed at screening. An additional ECG and supine blood pressure measurement were performed on the day of biopsy (Day 5 to 7) and on the day of surgery. CCI [redacted] CCI Blood and plasma samples for circulating tumour deoxyribonucleic acid (ctDNA) were collected at screening, on day of biopsy and the day of surgery. An additional blood sample (plasma and serum) to assess exploratory biomarkers was also collected at screening, on the day of biopsy and on the day of surgery. Patients were recruited until 12 evaluable paired biopsies were collected within each treatment group. Blood samples were collected for pharmacokinetic (PK) assessment on the day of biopsy. After the treatment period, patients had a 28-day safety follow-up visit by telephone to report any AEs and the use of concomitant medication.

Stage 2

Following the completion of the last patient visit in Stage 1 and availability of the immunohistochemistry (IHC) data, the Safety and Data Monitoring Committee (SDMC) convened to review the Stage 1 data, potentially alongside the emerging data from any relevant ongoing camizestrant studies. The SDMC made a decision to proceed with Stage 2 and the SDMC selected the number of treatment groups and doses. After the screening visit and confirmation of eligibility, patients were randomly assigned in a 1:1 (UK; 75 mg or

150 mg) or 1:1:1 (Mexico and Georgia; 75, 150, and 300 mg) ratio to receive one of the following 2 or 3 treatments (based on the geographical stratification factor):

- Camizestrant (75 mg, for 5 to 7 days)
- Camizestrant (150 mg, for 5 to 7 days)
- Camizestrant (300 mg, for 5 to 7 days)

Following randomisation, treatment was administered for 5 to 7 days, and the same schedule of assessments was followed as in Stage 1.

Stage 3

Based on data from Stages 1 and 2, the SDMC advised examination of the pharmacodynamic (PD) effects of different doses of camizestrant after longer treatment durations in Stage 3 of the study. As there were no apparent differences in PD effects between 150 and 300 mg camizestrant, the SDMC recommended that it would be appropriate to test the extended dosing period at 75 and 150 mg camizestrant only.

After the screening visit and confirmation of eligibility, patients were randomly assigned in a 1:1 ratio to receive one of the following 2 treatments:

- Camizestrant (75 mg, 12 to 15 days)
- Camizestrant (150 mg, for 12 to 15 days)

During the treatment period, patients attended study visits on Day 1, Day 7 (+ 3 days), day of biopsy (Day 12, 13, 14, or 15), day of surgery (following a washout from camizestrant for at least 5 days). In the event that a patient was undergoing longer-term neoadjuvant therapy rather than surgery, the 'surgery day' visit was to be conducted on the sixth day following the last dose of camizestrant (with a + 3-day window). If, at the Day 7 (+ 3 days) visit, a patient was observed to have a CCI [redacted], the patient was scheduled to undergo the biopsy day visit at Day 12; the patient then commenced the washout from camizestrant following the dose on Day 12. In the event that it was not possible to schedule the biopsy on Day 12, the patient began the washout immediately at the Day 7 (+ 3 days) visit and was not required to undergo biopsy. Patients were recruited until approximately 24 evaluable paired biopsies were collected within each treatment group of Stage 3. A treatment window of 12 to 15 days, along with a washout period of 5 days was considered to permit curative intent surgery within existing standard of care timeframes. Throughout the study, patients were asked to report AEs and the use of concomitant medications. Safety assessments (physical examination, vital signs, ECGs, clinical safety laboratory assessments) were performed at screening. An additional ECG and supine blood pressure measurement was performed at the Day 7 (+ 3 days) visit, on the day of biopsy (Day 12 to 15) and on the day of surgery. Patients wore a portable HR monitor continuously from Day 1 to the Surgery Visit

day. Blood and plasma samples for ctDNA were collected at screening, on the day of biopsy and the day of surgery. An additional blood sample (plasma and serum) to assess exploratory biomarkers were also be collected at screening, on the day of biopsy and on the day of surgery. After the treatment period, patients had a 28 day (± 3 days) safety follow-up visit by telephone to report any AEs and the use of concomitant medication.

Target Population and Sample Size

The study enrolled post-menopausal women aged at least 18 years with newly diagnosed, primary, invasive, ER-positive, HER2-negative breast cancer, scheduled to undergo treatment with curative intent by surgery and irrespective of clinical node status.

The study was designed as an estimation of ER knockdown by different camizestrant doses, as assessed by the manual H-score method. The sample size was based on the primary endpoint, percent change from baseline in ER expression in each dose group. Assuming a drop-out rate of 15%, approximately 14 patients were planned to be recruited per treatment group, to allow 12 evaluable patients per treatment group for the analysis of the primary endpoint at the end of Stage 1.

For Stage 1, a total of 12 evaluable patients per treatment group provided an 80% chance of obtaining an 80% confidence interval (CI), where one half of the CI was at most 14 for the mean percent change from baseline in ER. This was under the assumption of a true standard deviation of 29 (Robertson JF et al. Proliferation and AKT activity biomarker analyses after capivasertib (AZD5363) treatment of patients with ER+ invasive breast cancer (STAKT). Clin Cancer Res 2020;26:1574-85; Robertson JF et al. A randomised, window of opportunity study comparing the effects of the novel oral SERD AZD9496 with fulvestrant in patients with ER+ HER2- primary breast cancer. Clin Cancer Res 2020).

Following the SDMC review of Stage 1 data, approximately 24 evaluable patients were planned to be recruited to each of Group 1 (camizestrant 75 mg) and Group 2 (camizestrant 150 mg), and approximately 12 evaluable patients to Group 3 (camizestrant 300 mg).

In Stage 2 of the study, 12 patients in Group 1 (camizestrant 75 mg) and Group 2 (camizestrant 150 mg) were planned to be recruited from the UK to enable additional understanding of the homogeneity of the dose-response curves across the 2 geographies. The operating characteristics with 12 patients per dose group mirrored the Stage 1 precision above.

For completeness, with further patients recruited to the same 2 dose groups under Stage 2 of the study, approximately 36 evaluable patients could be included. A total of 36 evaluable patients per treatment group provided an 80% chance of obtaining an 80% CI where one half of the CI was at most 7 for the mean percent change from baseline in ER.

For Stage 3, a total of 24 evaluable patients per treatment group provided an 80% chance of obtaining an 80% CI, where one half of the CI is at most 9 for the mean percent change from baseline in ER. In relation to the key secondary endpoint of antigen Ki67 (Ki67), a total of 24 evaluable patients per treatment group provided an 80% chance of obtaining an 80% CI, where one half of the CI was at most 0.312 on the log scale, which if a geometric mean of -80% for Ki67 was observed, the expected CI would have been (-85%, -73%). CCI [redacted]
CCI [redacted]
CCI [redacted]

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

Study treatments are presented in Table S2.

Table S2 Study Treatments in Stage 1, Stage 2, and Stage 3

	Treatment 1	Treatment 2	Treatment 3 (Stage 2 Only)
Treatment name	Camizestrant		
Dosage formulation	CCI [redacted] tablets		
Dosage level(s)	75 mg once daily	150 mg once daily	300 mg once daily
Route of administration	orally		
Dosing instructions	CCI [redacted] tablets	CCI [redacted] tablet CCI [redacted] tablets	CCI [redacted] tablets
Packaging and labelling	Camizestrant was provided in bottles. Each bottle was labelled in accordance with country regulatory requirements.		
Provider	AstraZeneca		

Ten batches of camizestrant were used in this study. Individual batch numbers and further information are included in the CSR (Appendix 16.1.6).

Duration of treatment

Patients in Stages 1 and 2 received camizestrant for 5 to 7 days.

Patients in Stage 3 received camizestrant for 12 to 15 days.

Statistical methods

Analyses were performed by AstraZeneca or its representatives, including Clinical Research Organisations. All report outputs were produced using SAS® version 9.4 in a secure and validated environment.

All data were summarised by treatment group and time point. Stages 1 and 2 data combined, and Stage 3 data alone were reported separately. Continuous data were reported using descriptive statistics (number of patients [n], mean, standard deviation [SD], median, 25th and 75th percentile [wherever appropriate], minimum, and maximum values unless otherwise stated). Categorical data were reported using number of patients providing data at a relevant time point (n), frequency counts and percentages. A comprehensive Statistical Analysis Plan was developed and finalised before database lock and described the patient populations included in the analyses, and procedures for accounting for missing, unused, and spurious data.

A patient was evaluable for the primary endpoint if:

1 Patient had taken a minimum of 5 consecutive daily doses of camizestrant for Stages 1 and 2 prior to, and including, the biopsy day, and a minimum of 12 consecutive daily doses for Stage 3 prior to, and including, the biopsy day.
2 Patient received the last dose of camizestrant within 12 hours of on-treatment biopsy.
3 Biopsy pair evaluable as below:
   (a) The diagnostic and on-treatment biopsy pair was considered evaluable by central pathology assessment, defined as containing > 100 tumour cells in each formalin-fixed paraffin-embedded biopsy and
   (b) A minimum of 2 slides to allow measurement of ER.
4 Had no protocol deviations that may have impacted the biomarker analysis.

The following primary biomarker variable was calculated:

- Percent change from baseline in ER expression assessed by the manual H-score method after 5 to 7 consecutive days of camizestrant treatment for Stages 1 and 2, and after 12 to 15 consecutive days for Stage 3

The following secondary biomarker variables were calculated:

- Percent change from baseline in progesterone receptor (PgR) expression as assessed by manual H-score method after 5 to 7 consecutive days of camizestrant treatment for Stages 1 and 2, and after 12 to 15 consecutive days for Stage 3
- Percent change from baseline in Ki67 labelling index after 5 to 7 days of consecutive camizestrant treatment for Stages 1 and 2, and after 12 to 15 consecutive days for Stage 3

The primary endpoint (percent change from baseline in ER expression) and the secondary endpoints (percent change from baseline in PgR expression and change in Ki67 labelling index) were listed and summarised appropriately, based on the PD Analysis Set. An Analysis of Covariance (ANCOVA) model was fitted to each endpoint, with baseline value, day of

biopsy and dose group included in the model. Estimates of the least squares (LS) mean percent change taken from the model were presented together with 80% CIs. Normality of the data was assessed, and if it was judged that the data did not adequately follow a normal distribution, then the use of the natural log-transformed data (ratio) replaced the untransformed analysis as the primary approach. The distribution of the Ki67 index data was expected not to be normally distributed (Robertson JF et al. Proliferation and AKT activity biomarker analyses after capivasertib (AZD5363) treatment of patients with ER+ invasive breast cancer (STAKT). Clin Cancer Res 2020;26:1574-85; Robertson JF et al. A randomised, window of opportunity study comparing the effects of the novel oral SERD AZD9496 with fulvestrant in patients with ER+ HER2- primary breast cancer. Clin Cancer Res 2020), hence Ki67 index data were naturally log-transformed before being analysed.

Sensitivity analyses were conducted on a subset of the PD analysis set by excluding:

- From ER analysis:
  - Any patients who are HER2-positive by central assessment.
  - Any patients with an ER H-score < 10 on their pre-treatment biopsy.
- From PgR analysis:
  - Any patients who are considered to be HER2-positive by central assessment.
  - Any patients with a PgR H-score < 10 on their pre-treatment biopsy.
- From Ki67 labelling index analysis:
  - Any patients who are considered to be HER2-positive by central assessment.
- Any patients with a Ki67 labelling index < 5% from their pre-treatment biopsy.
- Any patients with an ER H-score < 10 on their pre-treatment biopsy.
- Any patients with an ER H-score < 10 on their pre-treatment biopsy or any patients with a Ki67 labelling index < 5% from their pre-treatment biopsy.

All safety analyses were performed on the Safety Analysis Set. Safety data were not analysed formally.

Safety and tolerability were assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs and ECGs. These were collected for all patients. Appropriate summaries of these data were presented.

Study Population

A total of 76 (Stages 1 and 2) and 59 (Stage 3) patients were randomised and received treatment. In Stages 1 and 2, 74 (97.4%) patients completed the study, and 2 (2.6%) patients were withdrawn from the study, one patient due to an AE (Coronavirus disease 2019 [COVID-19]) and one patient due to withdrawal by the patient. In Stage 3, 56 (94.9%) patients completed the study, and 3 (5.1%) patients were withdrawn: 2 (3.4%)

patients due to an AE and 1 (1.7%) patient due to consent withdrawal. The majority of patients were recruited from Georgia (Stages 1 and 2: 84.2%; Stage 3: 86.4%). Seven (9.2%) (Stages 1 and 2) and 4 (6.8%) (Stage 3) patients had at least 1 important protocol deviation (IPD); no IPDs were COVID-19-related. The COVID-19 pandemic had limited impact on patients enrolled but it may have affected the willingness of patients to participate in the study through impacts on broader healthcare provision. One (1.3%) patient in Stages 1 and 2 experienced disruptions due to the COVID-19 pandemic and as a result the patient withdrew from the study. No patients withdrew from the study due to COVID-19 disruptions in Stage 3.

The study population was as expected and representative of the intended target population of women with ER-positive HER2-negative primary breast cancer. Demographics and patient characteristics were broadly balanced across the treatment groups and stages. Histology types, ECOG performance status, American Joint Committee on Cancer stages of cancer, tumour grades, and Tumour (T) Lymph node (N) Metastases (M) staging of cancer classifications for primary tumours, regional lymph nodes, and distant metastases were broadly balanced across the treatment groups and stages. No patients took disallowed concomitant medications or had concomitant procedures performed during the study.

In Stages 1 and 2, 26, 31, and 11 patients were PD-evaluable in the camizestrant 75, 150, and 300 mg treatment groups, respectively. In Stage 3, 24 and 26 patients were PD-evaluable in the camizestrant 75 and 150 mg treatment groups, respectively.

Summary of Efficacy results

Not applicable.

Summary of PK results

PK observations in all stages were commensurate with steady-state predictions derived from previous studies.

Summary of PD results

The following conclusions are made based on the PD results obtained in this study:

Primary PD Endpoint - ER H-score:

For the primary PD variable of ER IHC expression, the percentage change in ER expression across Stages 1, 2, and 3 was as follows: -62.7%, -62.8%, and -67.1% for camizestrant 75, 150, and 300 mg doses, respectively, after 5 to 7 days of exposure, and -66.9% and -65.0% for camizestrant 75 and 150 mg doses, respectively, after 12 to 15 days of exposure. This demonstrates that the degree of ER degradation following camizestrant treatment is similar across 75, 150, and 300 mg doses, and durations of exposure.

Secondary PD Endpoint - PgR H-score:

For the secondary PD variable of PgR IHC expression, per sensitivity analysis, the percentage change in PgR expression across Stages 1, 2, and 3 was as follows: -35.2%, -44.0%, and -36.7% for camizestrant 75, 150, and 300 mg doses, respectively, after 5 to 7 days of exposure, and -61.8% and -55.0% for camizestrant 75 and 150 mg doses, respectively, after 12 to 15 days of exposure. This demonstrates that the degree of reduction in PgR expression following camizestrant treatment is similar across 75, 150, and 300 mg doses; a trend towards a greater reduction in PgR expression after longer exposures is noted, but with widely overlapping CIs.

Secondary PD Endpoint - Ki67 labelling index:

For the secondary PD variable of Ki67 labelling index, per sensitivity analysis, after 5 to 7 days of exposure, camizestrant at the 75 mg dose reduced Ki67 labelling index to a lesser degree than the 150 and 300 mg doses: -49.3%, -81.3%, and -78.9% for camizestrant 75, 150, and 300 mg doses, respectively. After 12 to 15 days of exposure, camizestrant at the 75 and 150 mg doses reduced Ki67 labelling index to a similar degree: -81.7% and -81.9% for camizestrant 75 and 150 mg doses, respectively.

Summary of safety results

All camizestrant doses were well tolerated in the early disease setting:

- There were no SAEs or deaths reported in the study.
- In Stages 1 and 2, 35 (46.1%) patients experienced an AE and 24 (31.6%) patients experienced AEs possibly related to treatment.
- In Stage 3, 30 (50.8%) patients experienced an AE and 27 (45.8%) patients experienced AEs possibly related to treatment.
- The majority of treatment-related AEs (TRAEs) at the patient level were of Common Terminology Criteria for Adverse Events (CTCAE) Grade 1. One (3.0%) patient reported a CTCAE Grade 3 TRAE (preferred term: diarrhoea) in the camizestrant 150 mg treatment group in Stage 2.
- There were no dose interruptions or dose modification due to AEs.
- Three patients reported AEs which led to discontinuation of treatment:
  - Stage 2, camizestrant 300 mg: Grade 1 COVID-19, not related to study treatment, discontinuation on Study Day 5.
  - Stage 3, camizestrant 150 mg: Grade 2 visual impairment, possibly related to study treatment, discontinuation on Study Day 3.
  - Stage 3, camizestrant 150 mg: Grade 1 bradycardia, possibly related to study treatment, discontinuation on Study Day 7.
- No clinically significant trends were observed in any laboratory values.

Conclusion(s)

SERENA-3 study demonstrated that the 75 mg dose of camizestrant achieves maximal levels of ER degradation, reduction of PgR expression (ER antagonism), and downstream inhibition of Ki67 labelling index (anti-proliferative effect).

Camizestrant at all doses examined (75, 150, and 300 mg) was well tolerated by patients with early breast cancer during the pre-surgical period.

SERENA-3 study data supports 75 mg as the optimal dose of camizestrant.