2 SYNOPSIS

Title of Study:	An Open-Label, Fixed Sequence Study in Healthy Post-Menopausal Female Subjects to Assess the Pharmacokinetics of Camizestrant (AZD9833) when Administered Alone and in Combination with Itraconazole	
Study Numbers:	Parexel Study No.: 274103 Sponsor Study No.: D8532C00003	
Investigational Medicinal Products:	Test Treatment: Camizestrant (AZD9833) + Itraconazole Reference Treatment: Camizestrant (AZD9833)	
Indication Studied:	Estrogen (ER)-Positive epidermal growth factor receptor 2 (HER2)-Negative Breast Cancer	
Development Phase:	Phase 1	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	PPD	
Study Centre:	Parexel Early Phase Clinical Unit - London	
Publication:	None	
Study Duration:	First subject first visit: 04 Oct 2022	Last subject last visit: 28 Dec 2022

Study Objective(s):

Primary objective:

To assess the effect of itraconazole on the pharmacokinetics (PK) of camizestrant.

Secondary objective:

To assess the safety and tolerability of camizestrant alone and in combination with itraconazole.

CCI [redacted]

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Study Design:

This was an open-label, fixed sequence study in healthy post-menopausal female subjects conducted at a single Clinical Unit.

The study comprised of:

- A screening Period of 28 days.
- Period 1:
  - Eligible subjects were admitted to the Clinical Unit on Day -1. On Day 1, subjects received a single oral dose of 75 mg camizestrant. CCI [redacted] Blood for camizestrant concentrations was collected at pre-dose and post-dose up to 72 h (Day 1 to Day 4).
  - There was a washout Period of 7 to 10 days between Period 1 and Period 2.
- Period 2:
  - Subjects were admitted to the Clinical Unit on Day -1. On Day 1, subjects received an oral dose of 200 mg itraconazole once in the morning and once in the evening. On Days 2 and 3, subjects received an oral dose of 200 mg itraconazole in the mornings only.
  - Subjects continued to stay in the Clinical Unit until Day 4 of Period 3.
- Period 3:
  - Period 3 immediately followed Period 2. On Day 1, subjects received a single oral dose of 75 mg camizestrant plus an oral dose of 200 mg itraconazole concomitantly in the morning. On Days 2 and 3, subjects received an oral dose of 200 mg itraconazole in the morning. Blood for camizestrant concentrations was collected at pre-dose on Day 1 and post-dose up to 72 h (Day 1 to Day 4).
- The subjects returned for a Follow-up Visit 7 to 14 days after the last camizestrant PK sample in Period 3.

Study Subjects:

Planned for Inclusion:	Enrolled:	Completed Study:
14 subjects	14 subjects	14 subjects

Main Inclusion Criteria:

The study was conducted in healthy post-menopausal female subjects aged 50 to 70 years, having a BMI between 19 and 35 kg/m^2 inclusive and weighing at least 50 kg and no more than 100 kg inclusive.

Investigational Medicinal Product(s):

Formulation:	IMP/NIMP	Strength/ Concentrations:	Batch/Manufacturing Lot Number:	Expiry Date:
Camizestrant (AZD9833)	IMP	75 mg/tablet	CCI [redacted]	CCI [redacted]
Itraconazole	NIMP	100 mg/capsule	CCI [redacted]	CCI [redacted]

Duration of Treatment:

Each subject was involved in the study for approximately 8 or 9 weeks (including a 28-day screening period).

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Treatment Compliance:

Dosing took place at the Parexel Early Phase Clinical Unit. Compliance was assured by direct supervision and witnessing of study intervention administration. After administration, a check of the subject's mouth and hands was performed.

The administration of all study intervention was recorded in ClinBase™.

Criteria for Evaluation:

Pharmacokinetic Parameters:

- Primary pharmacokinetic (PK) parameters: AUCinf, AUClast, and Cmax of camizestrant.
- Additional PK parameters: tmax, t½λz, λz, CL/F, Vz/F

Safety Variables:

- Adverse events (AEs), serious AEs (SAEs), AEs leading to the discontinuation of intervention (DAEs)
- Laboratory assessments (haematology, clinical chemistry, and urinalysis)
- Vital signs (supine pulse and blood pressure)
- Resting 12-lead electrocardiograms (ECGs)
- Physical examination.

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Statistical Methods:

Determination of Sample Size:

Fourteen subjects were enrolled into the study, to account for potential discontinuations. The number of subjects was based on the desire to gain adequate information on the primary objective of this study while exposing as few subjects as possible to the IMP and procedures.

The sample size calculation was based on the anticipated intra-subject variability and the desired precision within each arm. Interpretation of the results was based on the estimated geometric mean ratio and associated 90% CI between treatments for AUC and Cmax. If the true intra-subject coefficient of variation was 25%, then 11 evaluable subjects were expected to give a relative precision of 1.56 (ratio between the upper and lower limits of the 90% CI) with a probability of at least 80%. This corresponded to a 90% CI of 0.80 to 1.25 if the observed ratio was 1.

Presentation and Analysis of Pharmacokinetic Data:

The analyses of the PK variables were based on the PK analysis set. The PK parameters AUCinf, AUClast, and Cmax of camizestrant were analysed using an ANOVA model following a natural logarithmic transformation, with fixed effect for treatment and random effect for subject. Least-squares geometric means with 2-sided 95% CIs, ratios of geometric means together with 2-sided 90% CIs of test treatment (camizestrant + itraconazole), and reference treatment (camizestrant alone) were estimated and presented.

The rest of the PK parameters were presented by descriptive statistics.

Presentation and Analysis of Safety Data:

The analyses of the safety variables were based on the safety analysis set. All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarised using descriptive statistics (n, mean, SD, min, median, max) by treatment period. Categorical variables were summarised in frequency tables (frequency and proportion) by treatment/dose group.

Adverse events were summarised by Preferred Term and System Organ Class using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary. Furthermore, listings of SAEs and DAEs were made and the number of subjects who had any AEs, SAEs, DAEs, and AEs with severe intensity were summarised. Adverse events that occurred before dosing were reported separately.

Tabulations and listings of data for vital signs, clinical laboratory tests, and ECGs, were presented. Any new or aggravated clinically relevant abnormal medical physical examination findings compared to the baseline assessments were reported as an AE. Data were summarised for the observed values at each scheduled assessment, together with the corresponding changes (and/or percentage change) from the baseline when baseline was defined. Clinical laboratory data were reported in Système International units in this CSR.

Out-of-range values for the safety laboratory tests were flagged in individual listings as well as summarised descriptively using agreed reference ranges (eg, laboratory ranges).

Protocol Deviations:

There was one subject with an important protocol deviation. This subject had missing PK plasma sample for camizestrant measurement on Day 1 at 16 h post-dose. The 16 h post-dose PK sample was taken 20 hour post-dose due to difficult veins.

The reported deviation from the protocol did not have an effect on the interpretation of the study results nor did it lead to exclusion of any subject from the analysis populations.

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Pharmacokinetic Results:

- In the presence of itraconazole, systemic exposure to camizestrant increased by 37%, 74% and 90% for Cmax, AUClast, and AUCinf respectively.
- Median tmax for camizestrant was similar between treatments at 3.83 h for camizestrant administered alone, and 4.16 h for camizestrant in combination with itraconazole.
- Clearance and volume of distribution reduced by approximately 42% and 37%, respectively, and t½λz was longer in the presence of itraconazole (23.13 h vs 29.82 h).

Safety Results:

- There were no deaths or SAEs reported during the study.
- There were no AEs resulting in discontinuation of IP.
- No clinically meaningful trends were observed in haematology or clinical chemistry parameters, vital signs, or ECG parameters over time.
- Camizestrant when administered alone and in combination with itraconazole was well tolerated in healthy post-menopausal female subjects and there were no safety concerns observed.

Discussion and Conclusion:

- In the presence of itraconazole, systemic exposure to camizestrant increased by 37%, 74% and 90% for Cmax, AUClast, and AUCinf respectively.
- Camizestrant when administered alone and in combination with itraconazole was well tolerated in healthy post-menopausal female subjects and there were no safety concerns observed.

Version and date of report: 1.0 and 02 June 2023

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.