SERENA-1: Results from a Phase 1 study (Parts I/J) testing the next-generation oral selective estrogen receptor degrader (ngSERD) camizestrant (AZD9833) in combination with capivasertib in women with ER-positive, HER2-negative advanced breast cancer

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Introduction

- Camizestrant (AZD9833), ngSERD and pure ER antagonist, has shown anti-tumor activity in preclinical ER+ breast cancer models and demonstrated a statistically significant PFS benefit over fulvestrant in the Phase 2 SERENA-2 study(NCT04214288)[1–4]
- Capivasertib is a potent pan-Akt inhibitor with anti-tumour responses across models with or without detectable mutations or alterations in *PIK3CA, PTEN,* or *AKT*[5,6]
- In the Phase 3 CAPItello-291 trial in patients with HR+/HER2- ABC, the addition of capivasertib to fulvestrant compared with placebo plus fulvestrant resulted in statistically significant and clinically meaningful improvement in PFS[7]
- SERENA-1 (NCT03616587) is a first-in-human, multi-part, Phase 1 open-label study in heavily pre-treated women with ER+/HER2– ABC.[8] Data from Parts A/B, camizestrant monotherapy dose escalation and expansion;[8,9] Parts C/D, in combination with palbociclib;[9,10] and Parts G/H in combination with abemaciclib[11] have been previously reported
- Here, we present data from the ongoing SERENA-1 Parts I/J, investigating camizestrant in combination with capivasertib

Objectives

- **Primary objective:** To determine the safety and tolerability of camizestrant in combination with capivasertib
- **Secondary objectives:** Include anti-tumor activity, efficacy, and PK

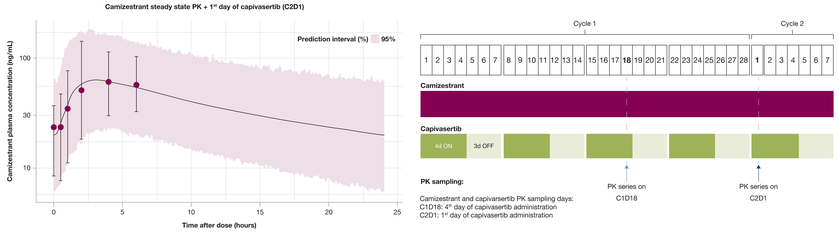
Methods

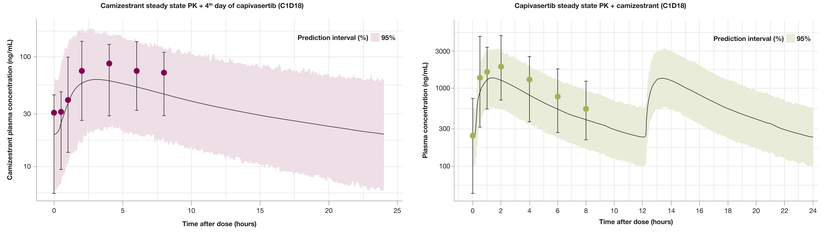
- Patients were previously treated women (any menopausal status) aged ≥18 years with ER+/HER2– ABC
  - Prior treatment with ≤2 lines of chemotherapy in the advanced setting was permitted
  - No limit on the number of lines of prior endocrine therapy in the advanced setting and no selection based on prior sensitivity to endocrine therapy
  - Prior treatment with CDK4/6i and/or fulvestrant was permitted
- Camizestrant was administered at a dose of 75 mg QD
- Capivasertib was administered at a dose of 400 mg BID (intermittent; 4d on/3d off)
- Preliminary efficacy was evaluated by ORR, CBR_{24}, and PFS
- Blood samples were collected at screening, C1D1, and C2D1 were assessed for the presence of *ESR1* mutations in ctDNA by next-generation sequencing
- PK sampling: C1D18: pre-dose, then 1, 2, 3, 4, 6, and 8h post dose. C2D1: pre-dose, 1, 2, 3, 4, and 6h post dose
- PK analysis: plasma concentrations of camizestrant and capivasertib multiple dosing were compared with population PK (popPK) model simulations. A within-patient comparison at C2D1 and C1D18 was performed to understand any difference in camizestrant PK between the 1st and 4th dose of capivasertib on a 4d on/3d off schedule

Pharmacokinetics

- Camizestrant steady state exposure in combination with the first day of capivasertib dosing on a 4d on/3d off schedule (C2D1) was in line with monotherapy popPK simulations. Camizestrant C_{max} and AUC_{0-8h} in combination with capivasertib on last day of 4d on/3d off schedule (C1D18) were 1.25 (95% CI: 1.08, 1.40) and 1.23 (95% CI: 1.06, 1.43) fold higher, respectively, when comparing within the same subjects at C2D1 (Figure 1)
- In combination with camizestrant, capivasertib steady state (C1D18) geometric mean C_{max} and AUC_{0-8h} values were 1.27 (95% CI: 0.99, 2.28) and 1.27 (95% CI: 0.86, 2.04) fold higher, respectively, than the popPK model predicted median (Figure 2)
- Considering the safety profile observed, the data do not suggest a clinically relevant DDI on either camizestrant or capivasertib exposure

Figure 1. Camizestrant 75 mg QD PK sampling and 75 mg plasma concentration at steady state in combination with capivasertib 400 mg





Points: median PK observations (N=16). Error bars: 2.5th and 97.5th percentiles of the data; Solid black line: median of popPK simulations* (N=1,000); Shadow: 95% prediction interval of popPK* simulations.
*PopPK model from PAGE 31 (2023) Abstr 10686 [www.page-meeting.org/?abstract=10686][12]

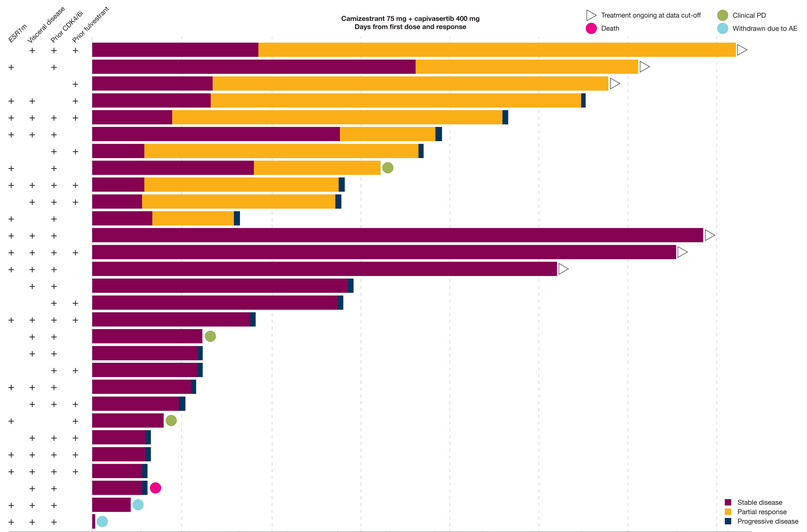
Figure 2. Capivasertib 400 mg BID plasma concentration at steady state in combination with camizestrant 75 mg QD

Points: PK observations (N=15). Error bars: 2.5th and 97.5th percentiles of the data. Solid black line: median of popPK* simulations (N=1,000); Shadow: 95% prediction interval of popPK* simulations.
*PopPK model built from PAGE 29 (2021) Abstr 9797 [www.page-meeting.org/?abstract=9797][13]

Clinical efficacy

- In these heavily pre-treated patients, with no selection for endocrine sensitivity, the clinical benefit rate was 51.7% (15/29) at 24 weeks (Figure 3)
  - CBR_{24} in patients with prior fulvestrant treatment was 56.3% (9/16)
  - CBR_{24} in patients with prior CDK4/6i treatment was 50.0% (13/26)
  - CBR_{24} in patients with detected *ESR1*m was 52.9% (9/17)
- ORR in patients with measurable disease was 37.0% (10/27)
  - Overall ORR was 34.5% (10/29) (incl. non-measurable disease)
- Median PFS was 8.5 months (95% CI: 4.7–16.4 [17/29])

Figure 3. Duration of patient exposure and response to camizestrant in combination with capivasertib

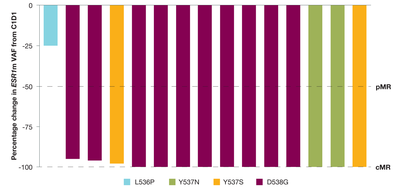


*ORR is defined as the percentage of patients with a confirmed investigator-assessed response of CR or PR and will be based on the evaluable per response set population. A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. CBR_{24} is defined as the proportion of patients who had a confirmed CR, PR, or stable disease lasting at least 24 weeks. Analysis was restricted to patients who had the opportunity to reach 24 weeks on treatment and included patients with both measurable and non-measurable disease at baseline.

*ESR1*m ctDNA dynamics

- 15 *ESR1*m variants were identified in 12 patients where C1D1 and C2D1 samples were analyzed, and an *ESR1*m was detectable in at least one sample. 14/15 (93.3%) variants were reduced by >50% by C2D1, including 11/15 (73.3%) variants which were cleared to undetectable levels. This included D538G and Y537S variants (Figure 4)

Figure 4. Percentage change in *ESR1*m variant allele frequency from C1D1



Conclusions

- Camizestrant 75 mg QD in combination with capivasertib 400 mg BID (4d on/3d off) is safe and well-tolerated, with a favorable PK profile indicating no clinically relevant DDI
- Despite extensive prior lines of therapy, including prior CDK4/6i, fulvestrant and/or chemotherapies, camizestrant in combination with capivasertib exhibited encouraging clinical activity, in addition to evidence of clearance of *ESR1*m ctDNA
- These data support the further investigation of camizestrant in combination with capivasertib in the treatment of patients with ER+/HER2– ABC

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Patient characteristics

- At the data cut-off (29-Sep-2023), 29 patients had received camizestrant in combination with capivasertib and 6 were still receiving therapy (Table 1)
  - 93% of patients had RECIST v1.1 measurable disease and 72% had visceral disease
  - The median number of prior treatment regimens in the advanced disease setting was 2 (range 1–6)
  - 55% of patients had received prior fulvestrant, and 90% had received prior CDK4/6i in the advanced setting
  - All patients received at least one prior ET regimen
  - The median duration of exposure to camizestrant in combination with capivasertib was 8.3 months (range 0–22)

Table 1. Patient characteristics

General characteristics	Camizestrant 75 mg + capivasertib 400 mg (N=29)
Median age, years (range)	53 (39–82)
Post-menopausal, n (%)	27 (93)
ECOG category 0, n (%)	13 (45)
Measurable disease, n (%)	27 (93)
Visceral disease, n (%)	21 (72)
Number of prior regimens in advanced setting, median (range)	2 (1–6)
Number of prior endocrine regimens in advanced setting, median (range)	2 (0–5)
Number of prior chemotherapy regimens in advanced setting, median (range)	0 (0–3)
Prior treatment with fulvestrant in advanced setting, n (%)	16 (55)
Prior treatment with CDK4/6i in advanced setting, n (%)	26 (90)
ESR1*m ctDNA baseline status, n (%)	
Detected	17 (59)
Not detected	12 (41)
Unknown	0

*ESR1m classed as D538G, Y537S/C/N/D, E380Q, L536R/H/P, S463P, V422del (mutation detected in the screening and/or C1D1 sample)

Safety and tolerability

- Safety and tolerability of camizestrant 75 mg in combination with capivasertib 400 mg was consistent with those of each drug individually (Table 2)
- No patient required camizestrant dose reduction or discontinuation
- Adverse events causally related to camizestrant (per investigator's opinion) led to dose interruptions in four (13.8%) patients. Table 3 displays all grade instances of possibly camizestrant- and/or capivasertib-related AEs (per investigator opinion) reported in ≥15% of patients:
  - One patient with Grade 3 diarrhea had a dose interruption of capivasertib followed by a dose reduction without recurrence of the AE
  - All cases of Grade 2 nausea were considered to be related to capivasertib (per investigator's opinion) but did not result in dose modification or interruption
  - Both cases of Grade 2 fatigue were considered to be related to camizestrant and capivasertib (per investigator's opinion) but did not result in dose modification or interruption
  - Maculopapular rash related to capivasertib was observed in three patients at Grade 2 and two patients at Grade 3. Capivasertib was interrupted in three patients (one Grade 2, two Grade 3), without camizestrant interruption. After recovery, two patients resumed capivasertib with no dose reduction and one patient resumed at a reduced dose of 320 mg
  - Grade 3 & 4 aspartate AST increase related to capivasertib were observed in 2 patients:
    - One patient reported Grade 3 AST increase in the context of sepsis and a G3 hyperglycaemia related to capivasertib per investigator's opinion and reported as an SAE. Both camizestrant and capivasertib were interrupted. Following resolution of sepsis and AEs, capivasertib was permanently discontinued, whereas camizestrant was resumed at the same dose without recurrence
    - One patient reported a Grade 4 AST increase considered related to capivasertib per investigator's opinion. This patient had a prior history of acute liver injury related to abemaciclib and baseline Grade 1 AST/ALT increases. Both camizestrant and capivasertib were interrupted. After recovery of AEs, camizestrant was resumed at the same dose level without recurrence. Capivasertib was permanently discontinued

Table 2. SERENA-1 camizestrant + capivasertib AE profile (irrespective of causality)

Preferred term	Camizestrant + capivasertib (n=29)		
	Any grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Diarrhea	22 (76)	3 (10)	–
Visual effects*	18 (62)	–	–
Nausea	13 (45)	–	–
Bradycardia	12 (41)	–	–
Fatigue†	9 (31)	–	–
AST increased	8 (28)	1 (3)	1 (3)
Rash‡	7 (24)	2 (7)	–
ALT increased	6 (21)	1 (3)	1 (3)
Anemia	6 (21)	1 (3)	–
Back pain	6 (21)	–	–
UTI	6 (21)	–	–
Vomiting	6 (21)	–	–
Constipation	5 (17)	–	–
Lymphopenia	5 (17)	–	–

*Visual effects includes the preferred terms: 'photophobia', 'vision blurred', 'visual impairment'. †Maximum Grade 3, so Grade 4 is not applicable. ‡Rash includes preferred terms: 'rash', 'rash macular', 'maculopapular rash', 'rash papular', 'rash pruritic'. §Grade 1 or 2 AEs related to both camizestrant and capivasertib (per investigator's opinion). –Represents no cases. AEs have been graded according to the National Cancer Institute CTCAE Version 4.03.

Table 3. AEs considered related to camizestrant or capivasertib (per investigator's opinion) in ≥15% of patients

Camizestrant-related AEs	Incidence and grading, n (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	2 (7)	0	0	0
Visual effects*	18 (62)	0	0	0
Bradycardia	12 (41)	0	0	0
Nausea	1 (3)	0	0	0
Fatigue	3 (10)§	2 (7)§	0	0
Rash‡	0	1 (3)§	0	0
AST increased	3 (10)	0	0	0
Capivasertib-related AEs				
Diarrhea	14 (48)	2 (7)	3 (10)	0
Visual effects*	3 (10)§	0	0	0
Bradycardia	2 (7)	0	0	0
Nausea	6 (21)	4 (14)	0	0
Fatigue	3 (10)§	2 (7)§	0	0
Rash‡	0	3 (10)	2 (7)	0
AST increased	3 (10)	0	1 (4)	1 (4)

Abbreviations

ABC: advanced breast cancer
AE: adverse event
ALT: alanine aminotransferase
AST: aspartate aminotransferase
AUC: area under curve
BID: twice daily
C: Cycle
CBR_{24}: clinical benefit rate at 24 weeks
CDK4/6i: cyclin-dependent kinase 4/6 inhibitor
C_{max}: maximum concentration
cMR: complete molecular response
CR: complete response
CTCAE: common terminology criteria for adverse events
ctDNA: circulating tumor DNA
D: Day
DDI: drug–drug interaction
ECOG: Eastern Cooperative Oncology Group
ER: estrogen receptor
ESR1: estrogen receptor 1 gene
*ESR1*m: estrogen receptor 1 gene mutation
ET: endocrine therapy
HER2: human epidermal growth factor receptor 2
HR: hormone receptor
ORR: objective response rate
PD: progressive disease
PFS: progression-free survival
PK: pharmacokinetics
pMR: partial molecular response
popPK: population pharmacokinetics
PR: partial response
QD: once daily
RECIST: Response Evaluation Criteria in Solid Tumors
SAE: serious adverse event
ngSERD: new generation selective estrogen receptor degrador
UTI: urinary tract infection
VAF: variant allele frequency

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