SERENA-1: Updated analyses from a Phase 1 study (Parts G/H) of the next-generation oral selective estrogen receptor degrader (SERD) camizestrant (AZD9833) in combination with abemaciclib, in women with ER-positive, HER2-negative advanced breast cancer

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Introduction

- Camizestrant (AZD9833) is a next-generation oral SERD that has shown anti-tumor activity in a range of preclinical models of ER+ breast cancer.[1,2]
- Clinical activity of camizestrant has also been demonstrated in SERENA-1 (NCT03616587)[3] and SERENA-2 (NCT04214288).[4,5] SERENA-1 is a first-in-human Phase 1, open-label study in heavily pre-treated women with ER+/HER2– ABC.[3]
- Data from SERENA-1 investigating camizestrant in a dose-escalation and randomized dose-expansion format as monotherapy (Parts A/B)[3] and in combination with palbociclib (Parts C/D)[6,7] have been previously reported.
- Here, we present data from the ongoing SERENA-1 Parts G/H, investigating camizestrant 75 mg in combination with abemaciclib 150 mg, a dose combination which is also under investigation in the Phase 3 SERENA-6 (NCT04964934) study.[8]

Objectives

- **Primary objective:** To determine the safety and tolerability of camizestrant in combination with abemaciclib.
- **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.
  - There was 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.
- Abemaciclib was administered at an initial dose of 150 mg BD. Dose modification, secondary to AEs, was in accordance with its relevant regional label.[9]
- Preliminary efficacy was evaluated by ORR, CBR24, and PFS.
- Blood samples collected at screening, Cycle 1 Day 1, and Cycle 2 Day 1 were assessed for the presence of *ESR1* mutations in ctDNA by next-generation sequencing. The limit of detection was 0.2% variant allele fraction.
- PK sampling: C1D1 (single dose): pre-dose, 1h, 2h, 3h, 4h, 6h, 8h, and 24h post-dose. C1D15 (steady state): pre-dose*, 1h, 2h, 3h, 4h, 6h, and 8h post-dose.
- Analysis: Plasma concentrations of camizestrant and abemaciclib after single and multiple dosing were compared with population PK (popPK) model simulations.

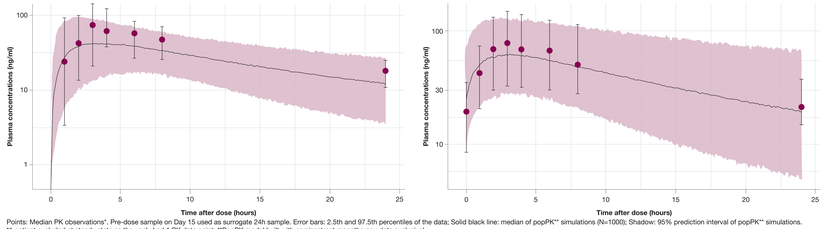
*The pre-dose sample on D15 was used as a 24h post-dose sample.

Pharmacokinetics

- Analysis of camizestrant 75 mg PK in combination with abemaciclib 150 mg (Figure 1) demonstrated that although Day 1 exposure appeared slightly higher than the predicted median, the majority (83%) of individual PK profiles were within the 95% prediction interval (Figure 1a). At steady state, the majority (89%) of observed plasma concentrations were within the 95% prediction interval, indicating no clinically meaningful DDI affecting camizestrant (Figure 1b).
- Analysis of abemaciclib 150 mg PK in combination with camizestrant 75 mg (Figure 2) demonstrated that although Day 1 exposure appeared higher compared with the median of the simulations (Figure 2a), the plasma concentrations at steady state were well distributed around the median. The majority of the data were included in the 90% prediction interval, suggesting no clinically meaningful DDI affecting abemaciclib (Figure 2b).

Figure 1. Camizestrant 75 mg plasma concentrations after a single dose and at steady state

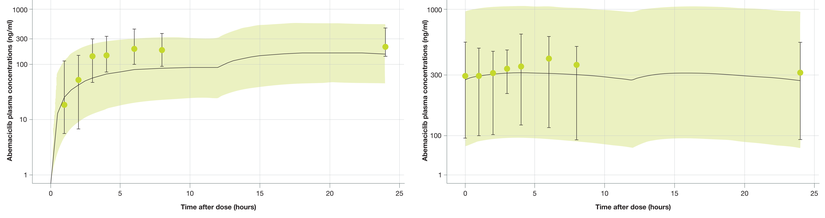
1a. Camizestrant PK after single dose **1b. Camizestrant PK at steady state**



Points: Median PK observations*. Pre-dose sample on Day 15 used as surrogate 24h sample. Error bars: 2.5th and 97.5th percentiles of the data; Solid black line: median of popPK** simulations (N=1000); Shadow: 95% prediction interval of popPK** simulations.
*1 patient excluded at steady state as they only had 1 PK data point; **PopPK model built with camizestrant monotherapy data exclusively.

Figure 2. Abemaciclib 150 mg plasma concentrations after a single dose and at steady state

2a. Abemaciclib PK after single dose **2b. Abemaciclib PK at steady state**

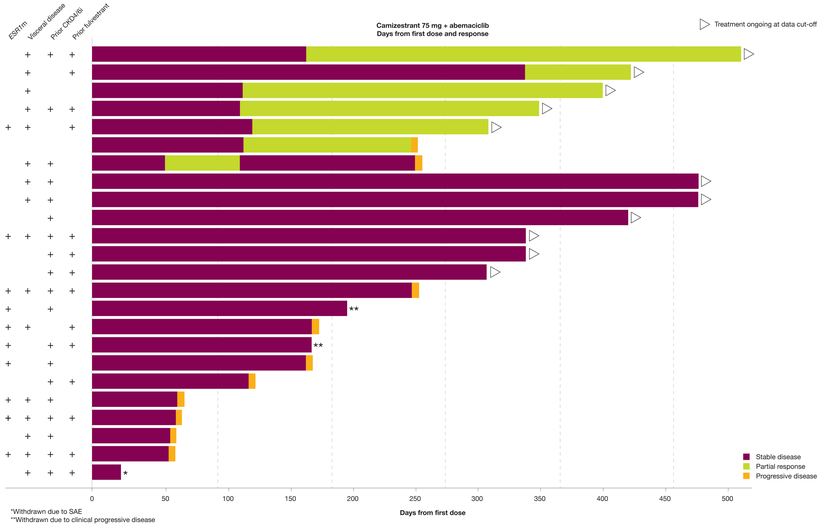


Points: PK observations*. Pre-dose sample on Day 15 used as surrogate 24h sample. Error bars: 2.5th and 97.5th percentile of the data. Solid black line: median of popPK** simulations (N=1000); Shadow: 90% prediction interval of popPK** simulations.
*4 patients were excluded due to dosing issues **PopPK model from the literature.[10]

Clinical efficacy

- In these heavily pre-treated patients, with no selection for endocrine sensitivity, the clinical benefit rate was 66.7% (16/24) at 24 weeks (Figure 3).
  - CBR_{24} in patients with prior fulvestrant treatment was 64.3% (9/14).
  - CBR_{24} in patients with prior CDK4/6i treatment was 63.2% (12/19).
  - CBR_{24} in patients with detected *ESR1*m was 50% (5/10).
- ORR in patients with measurable disease was 26.3% (5/19).
  - Overall ORR was 20.8% (5/24) (incl. non-measurable disease).
- Median PFS calculation not possible due to insufficient progression events.

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

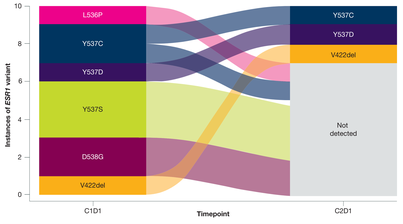


*Withdrawn due to SAE
**Withdrawn due to clinical progressive disease

ESR1 ctDNA dynamics

- In 70% of patients, *ESR1* mutations detectable in ctDNA at baseline were cleared to undetectable levels by C2D1 (Figure 4). The majority of *ESR1*m variant types detected were cleared.

Figure 4. Patients with C1D1 and C2D1 samples and detectable *ESR1* mutations at C1D1 and/or C2D1 (n=8). All mutations shown



Conclusions

- This Phase 1 dataset confirms the favorable PK and safety and tolerability profile of camizestrant 75 mg in combination with abemaciclib.
- PK data for camizestrant 75 mg plus abemaciclib were broadly consistent with camizestrant as monotherapy and published abemaciclib steady-state PK data, indicating no clinically meaningful DDI.
- Despite extensive prior lines of therapy in this patient population, including prior CDK4/6i, fulvestrant and chemotherapies, camizestrant in combination with abemaciclib exhibited encouraging clinical activity, including clearance of *ESR1*m ctDNA.
- These data support the use of camizestrant in combination with abemaciclib in the treatment of patients with ER+/HER2– ABC, including in the ongoing Phase 3 study SERENA-6 (NCT04964934) in first-line patients with ER+/HER2– ABC and detectable *ESR1*m.

Patient characteristics

- At the data cut-off (Aug 16, 2022), 24 patients had received camizestrant 75 mg in combination with abemaciclib (Table 1) and 11 were still receiving therapy.
  - The first patient was dosed on March 25, 2021.
  - 79% of patients had RECIST v1.1 measurable disease and 67% had visceral disease.
  - The median number of prior treatment regimens in the advanced disease setting was 3 (range 1–7).
  - In the advanced setting, 54% of patients had received prior fulvestrant and 75% had received prior CDK4/6i.
  - The median duration of exposure to camizestrant 75 mg in combination with abemaciclib was 8.7 (range 0–17) months.

Table 1. Patient characteristics

General characteristics	Camizestrant 75 mg + abemaciclib (N=24)
Median age, years (range)	61 (39–89)
Post-menopausal, n (%)	22 (92)
ECOG category 0, n (%)	11 (46)
Measurable disease, n (%)	19 (79)
Visceral disease, n (%)	16 (67)
Number of prior chemotherapy regimens in advanced setting, median (range)	1 (1–2)
Number of prior endocrine regimens in advanced setting, median (range)	2 (1–5)
Number of prior regimens in advanced setting, median (range)	3 (1–7)
Prior treatment with fulvestrant in advanced setting, n (%)	13 (54)
Prior treatment with CDK4/6i in advanced setting, n (%)	18 (75)
ESR1*m ctDNA baseline status, n (%)	
Detected	10 (42)
Not detected	12 (50)
Unknown	2 (8)

*ESR1m classed as E380Q, V422del, S463P, L536H/P/R, Y537C/D/N/S, D538G.

Safety and tolerability

- Safety and tolerability of camizestrant 75 mg in combination with abemaciclib was consistent with those of each drug individually.[6,9]
- No patient required camizestrant dose reduction.
- One patient experienced 2 SAEs possibly related to camizestrant per investigator opinion. The patient had not received study treatment for 3 weeks prior to onset and had a pre-trial diagnosis of hyperthyroidism which was well controlled. The SAEs comprised Grade 3 atrial fibrillation and Grade 2 thyrotoxicosis. The patient was discontinued from the trial.
- Table 2 displays Grade ≥2 instances of possibly camizestrant-related AEs (per investigator opinion) reported in ≥15% of patients.
- Of the 2 instances of Grade 2 nausea, both were also causally related to abemaciclib and neither resulted in camizestrant dose modification; the patients continued for 2 and 8 cycles, respectively, following AE onset before discontinuing due to progressive disease.
- One patient reported Grade 3 diarrhea that was also related to abemaciclib. Following dosing interruption, camizestrant and abemaciclib were restarted without and with dose reduction, respectively, and without recurrence of the AE during a further 3 cycles before discontinuation due to progressive disease.
- One patient experienced Grade 2 visual disturbance lasting 1 day and which resolved without dose modification. Another patient experienced photophobia, blurred vision, dry eye, and lacrimation (all Grade 2); camizestrant dosing was interrupted pending resolution and then resumed at the same dose and with no recurrence during 12 subsequent cycles (ongoing at data cut-off).
- Abemaciclib tolerability in combination with camizestrant appeared consistent with its known tolerability profile, including GI disorders, when combined with standard-of-care endocrine therapies (Table 3).

Table 2. Grade ≥2 instances of possibly camizestrant-related AEs (per investigator opinion) reported in ≥15% of patients

	Incidence and grading (n=24)
Visual effects	2 G2, 0 ≥G3
Dry eye	2 G2, 0 ≥G3
Nausea	2 G2, 0 ≥G3
Diarrhea	0 G2, 1 ≥G3

Causal association as per investigator opinion. Visual effects include the preferred terms: 'photophobia', 'vision blurred', and 'visual impairment'.

Table 3. SERENA-1 camizestrant + abemaciclib AE profile; comparison with MONARCH-2/3 data

	Camizestrant + abemaciclib (SERENA-1 G/H; n=24)			Fulvestrant or NSAI + abemaciclib (MONARCH-2/3; n=768)		
Preferred term	**Any grade**	**Grade 3**	**Grade 4**	**Any grade**	**Grade 3**	**Grade 4**
Diarrhea	20 (83.3)	2 (8.3)	–	650 (84.6)	90 (11.7)	–
Neutropenia	11 (45.8)	9 (37.5)	–	346 (45.1)	176 (22.9)	19 (2.5)
Nausea[a]	9 (37.5)	–	–	334 (43.5)	16 (2.1)	n/a
Fatigue[a]	11 (45.8)	2 (8.3)	–	311 (40.5)	18 (2.3)	n/a
Abdominal pain[a]	5 (20.8)	1 (4.2)	–	258 (33.6)	17 (2.2)	n/a
Anemia	6 (25.0)	–	–	231 (30.1)	54 (7.0)	1 (0.1)
Vomiting	7 (29.2)	1 (4.2)	–	213 (27.7)	9 (1.2)	–
Decreased appetite	8 (33.3)	–	–	203 (26.4)	10 (1.3)	–
Leukopenia	4 (16.7)	1 (4.2)	–	197 (25.7)	65 (8.5)	2 (0.3)
Alopecia[a]	3 (12.5)	–	–	159 (20.7)	n/a	n/a
Headache[a]	6 (25.0)	–	–	154 (20.1)	6 (0.8)	n/a
Blood creatinine increased	5 (20.8)	–	–	119 (15.5)	10 (1.3)	1 (0.1)
Constipation	–	–	–	117 (15.2)	5 (0.7)	–
Alanine aminotransferase increased	4 (16.7)	2 (8.3)	–	116 (15.1)	37 (4.8)	2 (0.3)

Pooled AE data from Monarch-2 & -3[11] with a reported incidence of ≥15%. [a]Maximum Grade 3, so Grade 4 is not applicable.[b]Maximum Grade 2, so Grades 3 or 4 are not applicable. SERENA-1 data: neutropenia include the preferred terms: 'neutropaenia' 'neutropenia' 'neutrophil count decreased'. Data presented as n (%). – Represents no cases, n/a: data not applicable.

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Abbreviations

ABC: advanced breast cancer
AE: adverse event
BD: twice daily
CBR24: clinical benefit rate at 24 weeks
C1D1: Cycle 1 Day 1
C2D1: Cycle 2 Day 1
CDK4/6i: cyclin-dependent kinase 4/6 inhibitor
ctDNA: circulating tumor DNA
DDI: drug–drug interaction
ECOG: Eastern Cooperative Oncology Group
ER: estrogen receptor
ESR1: estrogen receptor alpha gene
*ESR1*m: estrogen receptor alpha gene mutation
GI: gastrointestinal
HER2: human epidermal growth factor receptor 2
NSAI: non-steroidal aromatase inhibitor
ORR: objective response rate
popPK: population pharmacokinetics
PFS: progression-free survival
PK: pharmacokinetics
QD: once daily
RECIST: Response Evaluation Criteria in Solid Tumors
SAE: serious adverse event
SERD: selective estrogen receptor degrader

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