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ORIGINAL ARTICLE

A phase I dose escalation and expansion trial of the next-generation oral SERD camizestrant in women with ER-positive, HER2-negative advanced breast cancer: SERENA-1 monotherapy results

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Background: SERENA-1 (NCT03616587) is a phase I, multi-part, open-label study of camizestrant in pre- and post-menopausal women with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer. Parts A and B aim to determine the safety and tolerability of camizestrant monotherapy and define doses for clinical evaluation.

Patients and methods: Women aged ≥18 years with metastatic or recurrent ER+, HER2− breast cancer, refractory (or intolerant) to therapy, were assigned 25 mg up to 450 mg once daily (QD; escalation) or 75, 150, or 300 mg QD (expansion). Safety and tolerability, antitumor efficacy, pharmacokinetics, and impact on mutations in the estrogen receptor gene (*ESR1*m) circulating tumor (ct)DNA levels were assessed.

Results: By 9 March 2021, 108 patients received camizestrant monotherapy at 25-450 mg doses. Of these, 93 (86.1%) experienced treatment-related adverse events (TRAEs), 82.4% of which were grade 1 or 2. The most common TRAEs were visual effects (56%), (sinus) bradycardia (44%), fatigue (26%), and nausea (15%). There were no TRAEs grade 3 or higher, or treatment-related serious adverse events at doses ≤150 mg. Median t_{max} was achieved ∼2-4 h post-dose at all doses investigated, with an estimated half-life of 20-23 h. Efficacy was observed at all doses investigated, including in patients with prior cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) and/or fulvestrant treatment, with and without baseline *ESR1* mutations, and with visceral disease, including liver metastases.

Conclusions: Camizestrant is a next-generation oral selective ER antagonist and degrader (SERD) and pure ER antagonist with a tolerable safety profile. The pharmacokinetics profile supports once-daily dosing, with evidence of pharmacodynamic and clinical efficacy in heavily pre-treated patients, regardless of *ESR1*m. This study established 75-, 150-, and 300-mg QD doses for phase II testing (SERENA-2, NCT04214288 and SERENA-3, NCT04588298).

Key words: next-generation oral SERD, camizestrant, ER+ HER2− breast cancer

INTRODUCTION

Breast cancer is the most common cancer worldwide, accounting for 31% of new cancer diagnoses and 15% of cancer-related deaths in the United States in 2023 alone.[1,2] Approximately 80% of post-menopausal women with breast cancer have hormone receptor-positive (HR+) disease.[3,4]

Endocrine therapy is the mainstay treatment for HR+ breast cancer as it blocks estrogen receptor (ER)-driven signaling, reducing tumor growth.[5] Four main types of

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endocrine therapy are approved for treating breast cancer. These comprise selective ER modulators (SERMs), selective ER antagonists and degraders (SERDs), gonadotrophin-releasing hormone (GnRH) agonists, and aromatase inhibitors. Although these therapies can successfully disrupt ER signaling in tumors, intrinsic and acquired resistance remains challenging.[5-8]

A common resistance mechanism to current endocrine therapies is mutations in the estrogen receptor gene (*ESR1*m), which can result in constitutive activation of ER.[5] Disease with *ESR1*m often continues to rely on ER signaling for growth, but independent of estrogen itself; thus controlling ER activity remains a valuable therapeutic approach.[5,9]

Fulvestrant was the first approved SERD, a pure ER antagonist, due to its lack of agonism in all ER-positive (ER+) tissues.[10-12] Although fulvestrant has demonstrated clinical efficacy in patients with treatment-naive and treatment-resistant ER+ breast cancers, its low oral bioavailability necessitates administration by intramuscular injection, limiting dose delivery.[11,13,14] Consequently, as fulvestrant's pharmacodynamic (PD) activity is dose-dependent, the maximum achievable efficacy may be restricted.[8,12,14] An enhanced SERD that could achieve greater ER knockdown and inhibition of ER-signaling drive was hypothesized to deliver greater clinical efficacy.[13,14] Several novel SERDs have entered clinical development, including elacestrant (Radius and Menarini),[15] giredestrant (Roche),[16] imlunestrant (Lilly),[17] and amcenestrant (Sanofi).[18] However, early clinical results with these agents have been mixed, with positive data with elacestrant in the EMERALD study leading to its recent approval by the Food and Drug Administration, and negative randomized data in studies with giredestrant (acelERA) and amcenestrant (AMEERA-3).[15,16,18,19]

Camizestrant (AZD9833) is a next-generation oral SERD and pure ER antagonist, currently in phase III development for treating patients with HR+, human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer.[12,20] Preclinically, camizestrant demonstrated potent ER degradation activity and antitumor effects in both *ESR1* wild-type and mutant settings, with a predicted half-life supporting once-daily dosing in humans.[21]

SERENA-1 (NCT03616587) is an ongoing phase I, first-in-human, multi-center, dose-escalation and -expansion study designed to evaluate the safety and tolerability of camizestrant as monotherapy, and in combination with other novel anticancer agents, in women with ER+, HER2− advanced breast cancer. Here, we describe the results from the completed parts A and B of SERENA-1, which tested camizestrant as a monotherapy.

PATIENTS AND METHODS

Study compliance and oversight

This study was carried out in accordance with the principles of the International Conference on Harmonisation Guidelines for Good Clinical Practice, the Declaration of Helsinki, and all applicable national and local laws. All patients gave their written consent to participate before enrollment. The protocol was approved by the respective regulatory authorities and the research ethics committee of each participating site and was subject to Ethics Committee and Institutional Review Board approvals.

A safety review committee provided safety oversight and was responsible for dose-escalation and dose-expansion decisions after reviewing available study data.

Patient population

Participants were recruited at 17 sites in the UK, Spain, and the USA.

Eligible patients were pre- or post-menopausal women aged ≥18 years with metastatic or recurrent ER+, HER2− adenocarcinoma of the breast, refractory (or intolerant) to existing standard therapies. Pre-menopausal women must have been established on treatment with a luteinizing hormone-releasing hormone agonist for at least 4 weeks before receiving camizestrant, which was continued for the duration of the study treatment. Eligible patients must also have received prior treatment with ≥1 endocrine therapy but ≤2 chemotherapies in the advanced/metastatic disease setting. Prior treatment with cyclin-dependent kinase (CDK) 4/6 inhibitors was permitted.

Study design

SERENA-1 is an ongoing study with a multi-part design. In part A (dose escalation), eligible patients were assigned camizestrant at doses of 25 mg, 75 mg, 150 mg, 300 mg, or 450 mg once daily (QD). In part B (dose expansion), eligible post-menopausal patients were block randomized 1 : 1 : 1 to receive camizestrant 75 mg, 150 mg, or 300 mg once daily; a separate cohort of pre-menopausal patients was assigned to receive camizestrant 300 mg.

During dose escalation, the first patient in each cohort was followed up for at least 8 days before further patients were allocated to that cohort. When there were sufficient assessable patients for a dose-escalation decision (3-6 patients), there was a provision to both expand the current cohort (up to 12 assessable patients per cohort), and/or open a new cohort investigating a different camizestrant dose level, all per safety review committee agreement. A Bayesian logistic regression model incorporating instances of dose-limiting toxicities (DLTs) was used to model the dose toxicity response curve and inform subsequent dose level selections.[22]

Objectives and endpoints. The primary objective of SERENA-1 is to investigate the safety and tolerability of camizestrant in women with ER+, HER2− advanced breast cancer, and to define the dosing regimens for further clinical evaluation of camizestrant as monotherapy and in combination with other anticancer agents. Safety and tolerability endpoints include DLTs, adverse events (AEs), serious AEs (SAEs), vital signs, clinical chemistry/hematology parameters, and electrocardiograms (ECGs; reviewed centrally).

Secondary objectives include assessing the antitumor activity and efficacy of camizestrant, characterizing its single- and multiple-dose pharmacokinetics (PK), and investigating its PD activity in tumors. Exploratory objectives include investigating camizestrant activity through modulation of plasma circulating tumor DNA (ctDNA).

Assessments. Safety was assessed in terms of AEs, including treatment-emergent AEs (TEAEs), SAEs, treatment-related AEs (TRAEs; the reasonable possibility that the event may have been caused by camizestrant per investigator opinion), AEs leading to discontinuation, and AEs leading to death. Laboratory data, vital signs, and ECG changes were also assessed. AE severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. A safety review committee reviewed the safety, tolerability, and preliminary PK data, where available, from patients in each escalation cohort before opening the next dose cohort.

Plasma camizestrant concentration was determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method, with PK sampling time points as per Figure 1.

Objective tumor response assessment was based on the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guidelines.[23] Computed tomography/magnetic resonance imaging (CT/MRI) of the chest and abdomen was carried out in all patients at baseline (within 28 days of study start) and then at 8, 16, and 24 weeks after the start of treatment, and every 12 weeks thereafter until objective disease progression. A baseline bone scan or skeletal survey and follow-up visits were also carried out if clinically indicated. Objective response rate (ORR) was defined as the proportion of patients who had a complete response (CR) or partial response (PR) at any time during treatment, confirmed by repeat scans at least 4 weeks apart; analysis was restricted to patients with measurable disease at baseline.

PD effects of camizestrant in tumors were evaluated in paired biopsies provided by consenting patients. Expression of tumor biomarkers ERα, progesterone receptor (PgR), and Ki67 was assessed by immunohistochemistry to produce an H-score (ERα and PgR) or percentage of positive tumor cells (Ki67).

At screening, samples for ctDNA assessment were collected and then analyzed using a 500-gene next-generation sequencing (NGS) assay (GuardantOMNI™, Guardant Health, Palo Alto, CA). Plasma ctDNA samples collected at screening, cycle 1 day 1, and cycle 2 day 1 were analyzed using a custom 10-gene NGS assay (Resolution Bioscience Inc., Kirkland, WA). The custom assay was designed to detect substitutions, indels, and copy number alterations in the full coding region of eight genes (*AKT1, ARID1A, CDH1, ERBB2, GATA3, MAP3K1, PIK3CA, PTEN*) and selected regions of two genes (*ESR1* and *MYC*) using Resolution Bioscience bias-corrected targeted hybrid capture technology as previously described.[24] A patient was considered to have an *ESR1* mutation if an E380Q, V422del, S463P, L536H/P/R, Y537C/D/N/S, and/or D538G mutation was detected in either the screening or the cycle 1 day 1 sample, with no minimum variant allele frequency (VAF) cut-off.

RESULTS

The first patient in the monotherapy parts of SERENA-1 was dosed on 24 October 2018 and the final patient on 9 March 2021. Data cut-off was 9 September 2021, with 108 patients enrolled.

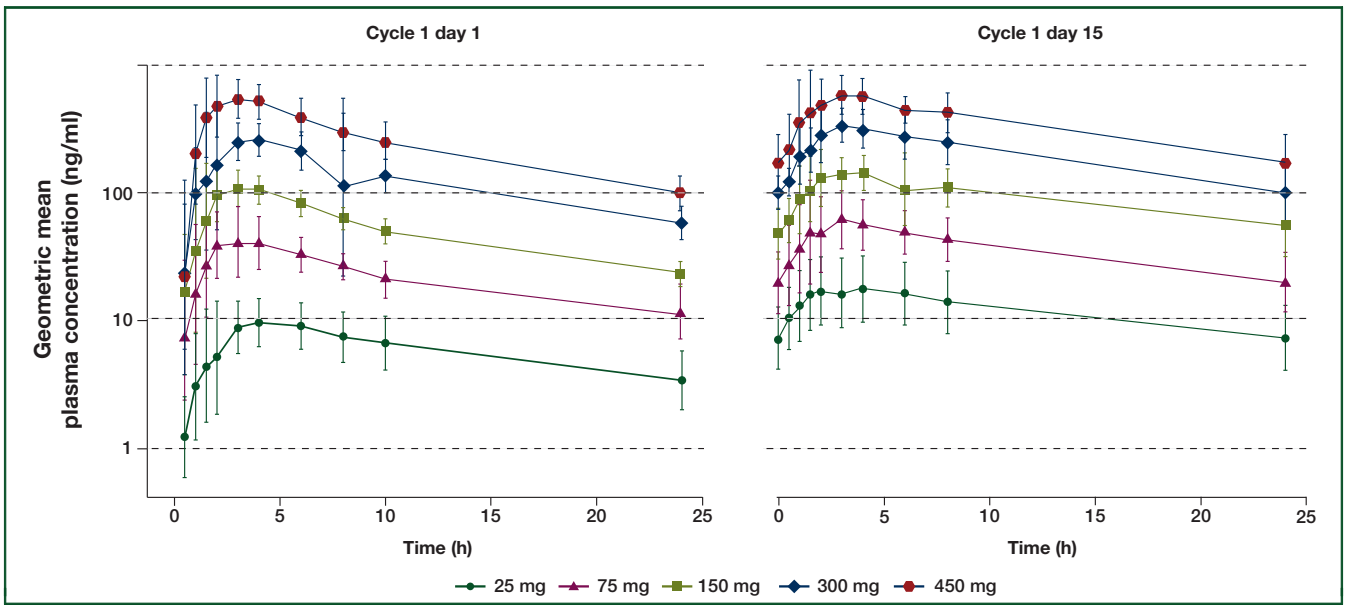

Figure 1. Geometric mean (± geometric standard deviation) plasma concentrations (ng/ml) of camizestrant versus time. Camizestrant (mg) following single dose (cycle 1 day 1) and multiple dosing (cycle 1 day 15).

Baseline characteristics

Patients had a median age of 61 years (Table 1). They were generally heavily pre-treated, with a median of three prior regimens received in the advanced setting, including a median of one prior chemotherapy regimen and a median of two endocrine therapies. Baseline *ESR1*m was detected in 49% (53/108) of patients. Respectively, 53% and 65% of patients had received prior fulvestrant and CDK4/6 inhibitors in the advanced disease setting. Overall, 79% of patients had RECIST-measurable disease at baseline, and 77% had visceral disease.

Safety

In total, 108 patients were treated across all camizestrant doses, with a mean [± standard deviation (SD)] treatment duration of 6.6 (±6.98) months (Table 2). Eleven patients were still receiving study treatment at the data cut-off. Patients who received at least one dose of camizestrant were included in the safety analysis set.

Overall, 100% of patients experienced at least one TEAE (Table 2), mostly CTCAE grade 1 or 2, with 25.9% of patients experiencing grade 3 AEs; no grade 4 or 5 TEAEs were reported during the study. The most common TEAEs of any grade were visual effects (61%), (sinus) bradycardia (44%), fatigue (35%), and nausea (30%).

Across the full dose range explored 25-450 mg, 93 patients (86%) experienced TRAEs, 82.4% of which were grade 1 or 2. The most common TRAEs of any grade were visual effects (56%), (sinus) bradycardia (44%), fatigue (26%), and nausea (15%). Distribution by dose and grade for these TRAEs is shown in Table 3. In the 75-mg cohort, 87.5% experienced a TRAE (all grade 1 or 2), of which visual effects (46%, all grade 1, i.e. not interfering with activities of daily living) and (sinus) bradycardia (29%, all grade 1 i.e. asymptomatic) were the most commonly reported.

TRAEs of CTCAE grade 3 or higher occurred in four (3.7%) patients overall: three patients at 300 mg, one patient at 450 mg. Treatment-related serious adverse events (TRSAEs) occurred in two (1.9%) patients, both in the 300-mg cohort (both also grade 3 TRAEs). Three (2.8%) patients experienced DLTs, one at 300 mg and two at 450 mg; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.04.012, provides further details for all TRSAEs, grade ≥3 TRAEs, and DLTs. There were no TRAEs of grade 3 or higher or TRSAEs at 150 mg or lower doses.

Overall, TRAEs led to dose reduction in six (6%) patients and to discontinuation in one (1%) patient (see Table 2). No camizestrant dose reduction or discontinuation secondary to TRAEs was reported for doses of 150 mg and below.

'Visual effects' was developed as a grouped concept term to encompass a range of vision-related preferred terms reported as AEs in SERENA-1, including photopsia and visual perseveration. Although these occurred with a dose-related incidence, visual effect AEs for camizestrant doses up to and including 150 mg were all grade 1 and, in no instance,

Table 1. Baseline patient demographics, disease characteristics, and duration of study treatment

Cohort	Camizestrant dose					
	25 mg	75 mg	150 mg	300 mg	450 mg	Total
N	12	24	25	35	12	108
Median age, years (range)	62 (39-74)	61 (41-83)	61 (43-81)	57 (36-79)	64 (40-81)	61 (36-83)
Post-menopausal, *n* (%)	12 (100)	23 (96)	24 (96)	25 (71)	11 (92)	95 (88)
ECOG category 0, *n* (%)	6 (50)	12 (50)	10 (40)	17 (49)	8 (67)	53 (49)
Measurable disease, *n* (%)	9 (75)	16 (67)	21 (84)	29 (83)	10 (83)	85 (79)
Visceral disease[a], *n* (%)	10 (83)	16 (67)	17 (68)	29 (83)	11 (92)	83 (77)
Liver visceral disease[b]	6 (50)	12 (50)	15 (60)	24 (69)	6 (50)	63 (58)
Lung visceral disease	7 (58)	4 (17)	4 (16)	12 (34)	4 (33)	31 (29)
Liver and lung visceral disease	3 (25)	1 (4)	2 (8)	7 (20)	0	13 (12)
Number of prior regimens in advanced setting, median (range)	3 (0-6)	2 (0-5)	3 (0-7)	2 (1-8)	4 (1-8)	3 (0-8)
Number of prior chemotherapy regimens in advanced setting, median (range)	1 (0-2)	0 (0-2)	1 (0-2)	1 (0-3)	2 (0-4)	1 (0-4)
Prior chemotherapy in advanced setting, *n* (%)	9 (75)	10 (42)	15 (60)	18 (51)	8 (67)	60 (56)
Number of prior endocrine regimens in advanced setting, median (range)	2 (0-3)	2 (0-5)	2 (0-6)	2 (0-5)	2 (1-6)	2 (0-6)
Prior treatment with fulvestrant in advanced setting, *n* (%)	7 (58)	7 (29)	14 (56)	22 (63)	7 (58)	57 (53)
Prior treatment with CDK4/6 inhibitors in advanced setting, *n* (%)	6 (50)	14 (58)	16 (64)	29 (83)	5 (42)	70 (65)
*ESR1*m ctDNA status at baseline[c], *n* (%)						
Not detected	8 (67)	9 (38)	11 (44)	19 (54)	6 (50)	53 (49)
Detected	4 (33)	15 (63)	13 (52)	15 (43)	6 (50)	53 (49)
Unknown	0	0	1 (4)	1 (3)	0	2 (2)

CDK4/6, cyclin-dependent kinase 4/6; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; *ESR1*m, mutations in the estrogen receptor gene.
[a]Visceral disease includes patients with disease site at baseline of adrenal, brain/central nervous system, esophagus, liver, lung/respiratory, pancreas, spleen, cardiovascular, gall bladder, gastrointestinal, genitourinary, and identified terms under other metastatic sites.
[b]Percentages calculated from the total number of subjects within the cohort.
[c]*ESR1*m defined as E380Q, V422del, S463P, L536H/P/R, Y537C/D/N/S, D538G.

Table 2. Adverse event summary

	Camizestrant monotherapy					
	25 mg ($N = 12$)	75 mg ($N = 24$)	150 mg ($N = 25$)	300 mg ($N = 35$)	450 mg ($N = 12$)	Total ($N = 108$)
Mean treatment duration, months (SD)	8.6 (9.70)	9.0 (8.05)	6.2 (7.37)	4.1 (3.80)	7.9 (6.50)	6.6 (6.98)
Any AE	12 (100.0)	24 (100.0)	25 (100.0)	35 (100.0)	12 (100.0)	108 (100.0)
Any TRAE	8 (66.7)	21 (87.5)	21 (84.0)	31 (88.6)	12 (100.0)	93 (86.1)
Any SAE	2 (16.7)	4 (16.7)	4 (16.0)	9 (25.7)	3 (25.0)	22 (20.4)
Any TRSAE	0	0	0	2 (5.7)	0	2 (1.9)
Any AE of CTCAE grade 3 or higher	4 (33.3)	4 (16.7)	6 (24.0)	11 (31.4)	3 (25.0)	28 (25.9)
Any causally related TRAE of CTCAE grade 3 or higher	0	0	0	3 (8.6)	1 (8.3)	4 (3.7)
AE leading to dose reduction	0	0	0	2 (5.7)	4 (33.3)	6 (5.6)
TRAE leading to dose reduction	0	0	0	2 (5.7)	4 (33.3)	6 (5.6)
Preferred term of TRAE leading to dose reduction				G1 Sinus bradycardia G2 Bradycardia	G1 Sinus bradycardia (x2) G3 Vomiting Combination of G1 asthenia, G2 gait disturbance, G2 headache, G1 nausea	
AE leading to discontinuation	0	0	1 (4.0)	3 (8.6)	0	4 (3.7)
TRAE leading to discontinuation	0	0	0	1 (2.9)	0	1 (0.9)
Preferred term of TRAE leading to discontinuation				G1 Sinus bradycardia		

Data presented as *n* (%).
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; G, grade; SAE, serious adverse event; SD, standard deviation; TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event.

resulted in dose modification. Visual effects, where reported, generally occurred within a few weeks of commencing treatment and, in all cases, fully resolved within a similar timescale following its cessation. Visual effects were typically experienced intermittently and for short durations, often associated only with transitions from darkness to bright light, with no alteration in severity grading over the treatment period. Comprehensive ophthalmological examinations, including assessment of visual fields, visual acuity, intraocular pressure, and fundoscopy, revealed no evidence of structural changes in the eye associated with camizestrant treatment.

Camizestrant treatment was associated with a dose- and time-dependent, reversible reduction in resting heart rate, with a gradual decrease to a stable nadir over ∼14 days, with maintained sinus rhythm. Reversion to baseline resting heart rate follows a profile that is broadly symmetrical with the onset profile following cessation of dosing. Bradycardia is a grouped concept term encompassing the preferred terms of bradycardia and sinus bradycardia and was reported in 44% (48/108) of patients across the full dose range explored 25-450 mg. Bradycardia reports for camizestrant at doses 25 mg to 75 mg were all grade 1. No instances of dose reduction or discontinuation arose from bradycardia TRAEs among patients on camizestrant doses of 150 mg or lower. In addition to conventional AE reporting, digital centrally read triplicate ECGs were used in SERENA-1; treatment with 75 mg and 150 mg camizestrant was associated with a mean change in heart rate nadir versus baseline of −12.5 bpm [95% confidence interval (CI) −16.0 to −9.0 bpm] and −13.5 bpm (95% CI −18.2 to −8.9 bpm), respectively. ECG data confirmed that camizestrant treatment was not associated with modulation of the PR or QRS interval, whilst ambulatory ECG data (incorporating nocturnal monitoring) provided no evidence of clinically significant abnormalities, including conduction pauses, consistent with the absence of an effect on cardiac conduction pathways. Furthermore, camizestrant treatment did not lead to changes in blood pressure, including in response to an orthostatic challenge, nor did serial echocardiograms reveal evidence of cardiac function modulation. Investigators reported preservation of the chronotropic response to informal exercise challenge.

The recorded effect of camizestrant on QT interval depended on the method used for heart rate correction. Camizestrant was associated with a time- and dose-dependent increase in the QT interval measured using the Fredericia method (QTcF), with a steady plateau reached over ∼14 days. As for bradycardia, reversion of QTcF intervals to baseline values follows an ∼14-day profile after camizestrant cessation. Conversely, using Bazett's method to measure the QT interval (QTcB), camizestrant

Table 3. TRAEs reported in ≥10% patients overall

Term	Camizestrant dose				
	25 mg ($N = 12$)	75 mg ($N = 24$)	150 mg ($N = 25$)	300 mg ($N = 35$)	450 mg ($N = 12$)
Visual effects	1 (8) G1: 1, G2: 0, G3: 0	11 (46) G1: 11, G2: 0, G3 :0	16 (64) G1: 16, G2: 0, G3: 0	25 (71) G1: 23, G2: 1, G3: 1	8 (67) G1: 7, G2: 1, G3: 0
Leading to dose reduction	0	0	0	0	0
Leading to discontinuation	0	0	0	0	0
Bradycardia	3 (25) G1: 3, G2: 0, G3: 0	7 (29) G1: 7, G2: 0, G3: 0	11 (44) G1: 9, G2: 2, G3: 0	17 (49) G1: 15, G2: 2, G3: 0	10 (83) G1: 9, G2: 1, G3: 0
Leading to dose reduction	0	0	0	2	1
Leading to discontinuation	0	0	0	1	0
Fatigue	3 (25) G1: 2, G2: 1, G3: 0	5 (21) G1: 4, G2: 1, G3: 0	7 (28) G1: 4, G2: 3, G3: 0	8 (23) G1: 5, G2: 2, G3: 1	5 (42) G1: 1, G2: 4, G3: 0
Leading to dose reduction	0	0	0	0	1
Leading to discontinuation	0	0	0	0	0
Nausea	2 (17) G1: 2, G2: 0, G3: 0	3 (13) G1: 2, G2: 1, G3: 0	0 (0)	7 (20) G1: 5, G2: 2, G3: 0	4 (33) G1: 1, G2: 3, G3: 0
Leading to dose reduction	0	0	0	0	1
Leading to discontinuation	0	0	0	0	0
Dizziness	1 (8) G1: 1, G2: 0, G3: 0	1 (4) G1: 1, G2: 0, G3: 0	4 (16) G1: 2, G2: 2, G3: 0	3 (9) G1: 2, G2: 0, G3: 1	2 (17) G1: 2, G2: 0, G3: 0
Leading to dose reduction	0	0	0	0	0
Leading to discontinuation	0	0	0	0	0

Data presented as *n* (%) reporting the corresponding AE.
CTCAE grading of corresponding AE presented as grade (G)1: number,G2: number,G3: number. No G4 or G5 TRAEs were reported in SERENA-1.
Terms represent MedDRA preferred terms, save for the hybrid terms as follows: Visual effects include the preferred terms 'visual perseveration', glare', 'photophobia', 'diplopia', 'vision blurred', 'photopsia', and 'visual impairment'; bradycardia includes the preferred terms 'bradycardia' and 'sinus bradycardia'; fatigue includes the preferred terms 'asthenia' and 'fatigue'.

treatment was associated with a time- and dose-dependent decrease in the QT interval. QTcF prolongation was reported in 10 patients overall: 1 at 25 mg (at grade 2), 1 at 75 mg (at grade 1), 3 at 150 mg (2 at grade 1, 1 at grade 2), 5 at 300 mg (4 at grade 1, 1 at grade 2), and none at 450 mg; there were no instances of grade 3+ QTcF prolongation at any dose. The median change in QTcF (ms) from baseline was 3.3, 2.2, 14.1, 18.0, and 17.6; the median change in QTcB (ms) from baseline was −3.6, −9.0, −10.8, −3.8, and −9.9, all following treatment with 25, 75, 150, 300, and 450 mg camizestrant, respectively. Work to better understand the effect, if any, of camizestrant on the QT interval is ongoing, including the use of individualized QT correction methodology.

ECG data revealed that greater reductions in resting heart rate were generally observed in patients with a higher baseline heart rate. Patients with a lower baseline heart rate had smaller reductions; accordingly, SERENA-1 eligibility has remained agnostic to baseline resting heart rate. SERENA-1 did not contraindicate concomitant medications with heart rate-lowering properties (e.g. beta-blockers). Patients receiving concomitant beta-blockers experienced no greater decrease in resting heart rate than patients not receiving them, and with no requirement for beta-blocker dose modification.

Camizestrant dosing was escalated to 450 mg without reaching the maximum tolerated dose; no further dose escalation was pursued from that point given that exposures 176-fold above target *in vitro* IC_{50} had been achieved at C_{min}.

Pharmacokinetics

After the first dose of camizestrant, the median t_{max} was achieved ∼2-4 h post-dose at all doses investigated (Figure 1 and Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.04.012). After reaching t_{max}, plasma concentrations declined with a geometric mean terminal elimination half-life of ∼10-15 h across all dose groups. This is likely an underestimate because PK was only sampled up to 24 h post-dose, making it difficult to fully characterize the terminal half-life. Indeed, data from a combined, unpublished population PK analysis of SERENA-1 data and a healthy volunteer study (NCT04546347) suggest the half-life is likely to be longer, at 20-23 h. Following the first dose on day 1, the C_{max} and area under the curve $(AUC)_{0\text{-}24}$ increased more than proportionally over the 25- to 450-mg range, with the 450-mg dose-normalized C_{max} and $AUC_{0\text{-}24}$ values 3.3- and 2.4-fold higher, respectively, than the 25-mg dose-normalized values.

After multiple dosing, the median t_{max} was achieved ∼2-4 h post-dose across the dose range investigated, as observed with the initial dose (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.04.012). There was evidence of some accumulation at all dose levels with the day 15/day 1 AUC and C_{max} ratios being 1.4- to 2-fold and 1.15- to 1.8-fold, respectively.

Efficacy

In this generally heavily pre-treated population, evidence of camizestrant efficacy was observed at all doses investigated, with an ORR of 15.3% (13/85), a clinical benefit rate at 24 weeks (CBR_{24}) of 35.2% (38/108), and a median progression-free survival (PFS) of 5.4 months (95% CI 2.6-7.2 months). In the 75-mg cohort, ORR was 18.8% (3/16), CBR_{24} was 54.2% (13/24), and median PFS was 7.3 months (95% CI 1.9-11.2 months) (Figure 2).

Clinical efficacy was also observed in the following groups of patients: with prior fulvestrant treatment, with prior CDK4/6 inhibitor treatment, with or without evidence of disease harboring *ESR1* mutations at baseline, and with visceral disease, including liver metastases. In patients with *ESR1*m detected at baseline and across all dose cohorts, ORR was 27.3% (12/44), CBR_{24} was 47.2% (25/53), and median PFS was 7.2 months (95% CI 5.3-11.1 months).

Pharmacodynamics

Paired pre- and on-treatment tumor biopsies were available for 21 patients (2 at 25 mg, 6 at 75 mg, 5 at 150 mg, 6 at 300 mg, 1 at 450 mg, and 1 patient who started at 450 mg and who was dose reduced to 300 mg before biopsy, was included in the 300-mg group). Samples were stained for immunohistochemical analysis of ERα, PgR, and Ki67; cases where pre-treatment ERα or PgR H-score was <10 or Ki67 percent positive was <5 were excluded from the percentage change from baseline analysis (Figure 3A). ERα levels were reduced in all cases, as was PgR in most cases. However, some profound changes in Ki67 were observed, including an 85% and 99% reduction in the two patients who provided paired biopsies and both achieved a PR (one patient on 75 mg and the other on 300 mg).

The impact of camizestrant treatment on *ESR1*m ctDNA levels was also assessed. Fifty-three (49%) patients had *ESR1*m detectable at baseline (screening and/or cycle 1 day 1; Table 1). Forty patients had a cycle 1 day 1 and a cycle 2 day 1 sample assessed, with an ESR1m variant detected in at least one sample. Of these, 18/40 (45%) had more than one variant detected, with 71 variants totally detected in these 40 patients. Across all doses tested, *ESR1*m levels were reduced by treatment, with 58/71 (82%) of detected variants reduced by 50% or more, including 42/71 (59%)

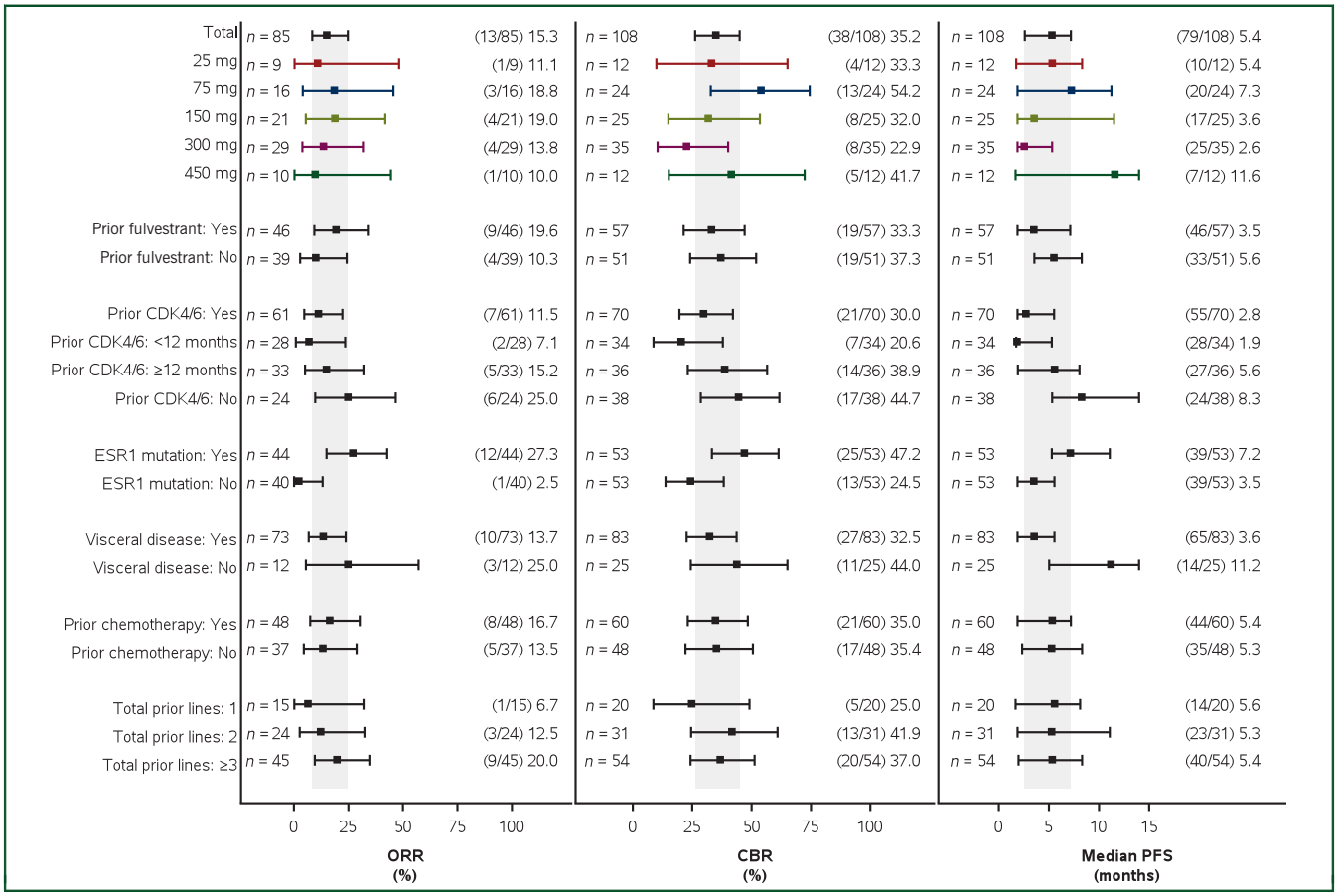

Figure 2. Combined efficacy plot of ORR, CBR_{24}, and median PFS for all doses and key subgroups. ORR and CBR_{24} plots represent percentage with binomial 95% confidence interval (CI). PFS plots represent median value (months) with 95% CI. For all plots, the gray shading represents 95% CI range for the total dataset. CBR_{24} is defined as the proportion of patients who had a confirmed best objective response of CR or PR in the first 25 weeks, or stable disease for at least 23 weeks from the start of study treatment. PFS was defined as the time from first dose until the date of objective disease progression or death (by any cause in the absence of progression), based on the investigator overall response, with medians derived using the Kaplan—Meier methodology, and summarized by dose. Participants who had not progressed or died at the time of analysis were censored at the date of their last evaluable RECIST assessment.

CBR_{24}, clinical benefit rate at 24 weeks; CDK4/6i: cyclin-dependent kinase 4/6 inhibitor; CR, complete response; *ESR1*, estrogen receptor 1 gene; ORR, overall response rate; PFS, progression-free survival; PR, partial response.

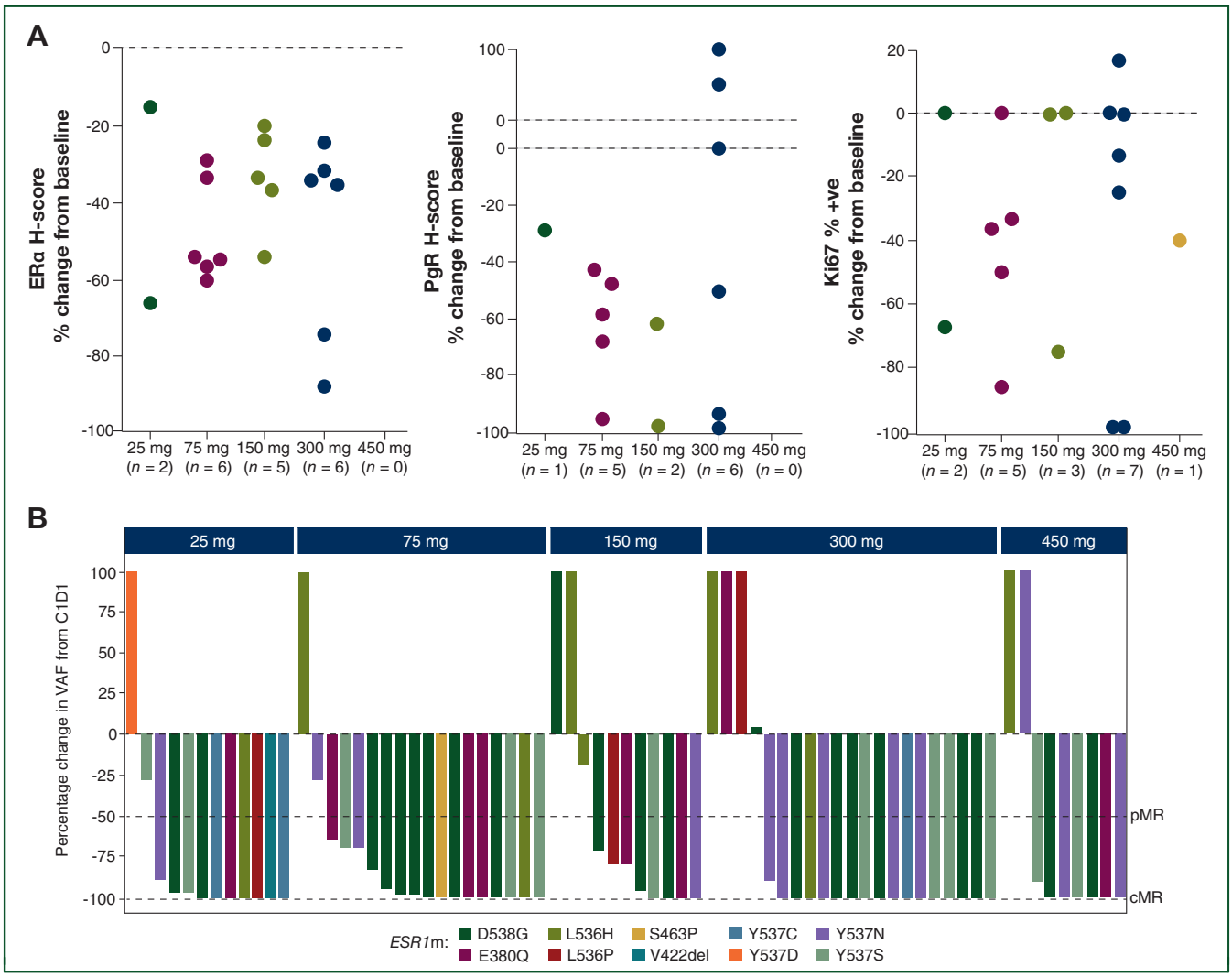

Figure 3. Pharmacodynamic analysis of paired tumor biopsies and ctDNA. (A) Paired tumor biopsies were collected at screening and cycle 2 day 1. Immunohistochemistry analysis was carried out for ERα, PgR, and Ki67. Change from baseline (%) is presented for individual patients. Cases where baseline ERα or PgR H-score was <10 or Ki67 percent positive was <5 were excluded. (B) Plasma samples were collected at cycle 1 day 1 and cycle 2 day 1 and the *ESR1*m VAF was determined by next-generation sequencing. Change in VAF (%) at cycle 2 day 1 compared with cycle 1 day 1 for each variant detected is presented. *ESR1*m was defined as a mutation that gives rise to one of the following amino acid changes: E380Q, V422del, S463P, L536H/P/R, Y537C/D/N/S, or D538G. Maximum increase in VAF is capped at 100%. ctDNA, circulating tumor DNA; ERα, estrogen receptor α; *ESR1*m, mutations in estrogen receptor 1 gene; PgR, progesterone receptor; VAF, variant allele frequency.

reduced to undetectable levels at cycle 2 day 1. This occurred across all the major *ESR1*m variants, including D538G, Y537S, Y537N, and E380Q (Figure 3B).

The association of clinical outcome and changes in total *ESR1*m ctDNA was also assessed (Supplemental Figure S1, available at https://doi.org/10.1016/j.annonc.2024.04.012). A total of 33 out of 40 (83%) patients had at least a 50% reduction in *ESR1*m, with 22/40 (55%) cases where *ESR1*m is reduced to undetectable levels. In general, patients with a longer PFS had greater reductions in *ESR1*m ctDNA at cycle 2 day 1. Also, of the 20 patients who received clinical benefit and 7 patients who had a response in this cohort of patients, 15 (75%) and 6 (86%), respectively, also cleared *ESR1*m ctDNA to undetectable levels.

DISCUSSION

The search for a more effective oral SERD resulted in the identification of camizestrant.[25] This molecule has demonstrated substantial and differentiated activity in preclinical studies, including in models resistant to current endocrine therapies.[21]

SERENA-1 has demonstrated that camizestrant has a tolerable safety profile over a wide dose range. The most commonly reported TRAEs in this study were transient visual effects, predominantly with ambient lighting change, (sinus) bradycardia, fatigue, and nausea, which were typically mild (grade 1 or 2) and manageable without dose modification. The investigators reported that patients with bradycardia could increase their heart rate with exercise, although formal exercise tolerance testing was not carried out in this population of patients with metastatic disease. Camizestrant dose escalation proceeded to 450 mg without defining a maximum tolerated dose. No instances of camizestrant dose reduction or discontinuation secondary to TRAEs were reported for doses of 150 mg or below, exemplifying the tolerability of camizestrant.

PK data confirmed the suitability of camizestrant for once-daily dosing. Doses of 25 mg QD and higher attained steady-state free C_{min} (~10 nM at 75 mg once daily) greater than the target IC_{50} calculated from *in vitro* studies (0.4 nM).[21] The moderate variability of measured PK parameters in SERENA-1, where patients could take camizestrant with or without food, was commensurate with the absence of a food effect. This was subsequently confirmed in a dedicated healthy volunteer study.[26]

These PK observations translated into concordant PD observations in terms of paired tumor biopsy data across the three key PD response markers assessed (ERα, PgR, and Ki67), as well as reductions in *ESR1*m ctDNA VAF including across all key *ESR1*m variants. While the data are relatively sparse, there is no indication of increased PD activity at higher doses of camizestrant.

In this heavily pre-treated setting, where patients had a median of three prior lines of therapy for advanced disease, clinical efficacy in terms of ORR, CBR24, and PFS was observed at all camizestrant doses tested, including in patients previously treated with CDK4/6 inhibitors and/or fulvestrant, and in patients with or without baseline-detectable *ESR1*m. Clinical efficacy appeared more pronounced in patients with detectable *ESR1*m, complemented by ctDNA analysis showing that *ESR1*m VAF was often reduced to undetectable levels. These data align with the phase III EMERALD trial, which investigated the oral SERD/SERM elacestrant in a similar population and found greater PFS benefit among patients with detectable *ESR1*m than in the overall population.[27]

In this late-line setting, it is likely that the presence of *ESR1*m identifies a patient population whose disease is still driven by ER signaling. Whilst the sample size at each dose level is relatively small in this phase I study, and the patient population was heavily pre-treated, no increases in clinical efficacy were noted at camizestrant dose levels above 75 mg, consistent with the absence of a strong PD trend with higher doses.

Key strengths of the monotherapy parts of SERENA-1 include its provision for a randomized expansion comparison in part B across the three doses of key interest following completion of part A, i.e. 75, 150, and 300 mg; the inclusion of paired biopsy sampling along with serial ctDNA collection across a wide range of doses; and the relatively broad study population, which permitted a preliminary view of safety and efficacy in patients with differences in prior and concomitant therapies, and for *ESR1*m-detected and not-detected subgroups. Some limitations common to phase I studies include the lack of a comparator, a heavily pre-treated population, which may have confounded the efficacy assessment, and the small sample size at each dose level, making conclusive statements regarding dose—response difficult.

SERENA-1 demonstrates that camizestrant has a well-tolerated safety profile, PK characteristics suitable for once-daily dosing, and evidence of PD and clinical efficacy in heavily pre-treated patients, including in those with *ESR1*m-detected and not detected. The study established that the doses of interest for phase II testing were 75, 150, and 300 mg QD.

The data from SERENA-1 is congruent with recent results from the randomized SERENA-2 phase II study (NCT04214288), which demonstrated a statistically significant and clinically meaningful PFS benefit for both camizestrant 75 mg and 150 mg doses versus fulvestrant, and in the context of an unchanged overall safety profile.[28,29] Further investigation of the biological effects of camizestrant at a range of doses in women with primary ER+, HER2− breast cancer is ongoing in the SERENA-3 (NCT04588298) study.

Camizestrant is currently under evaluation in several phase III randomized clinical trials. In patients with metastatic breast cancer: SERENA-4 (NCT04711252)[30] compares camizestrant and palbociclib versus anastrozole and palbociclib as an initial treatment for women with ER+, HER2− advanced breast cancer; SERENA-6 (NCT04964934)[31] compares the effects of camizestrant in combination with palbociclib, ribociclib, or abemaciclib versus anastrozole or letrozole in combination with palbociclib, ribociclib, or abemaciclib in patients with ER+, HER2− metastatic breast cancer with detectable *ESR1*m. Two phase III studies in early-stage ER+, HER2− breast cancer are also ongoing: CAMBRIA-1 (NCT05774951), comparing camizestrant versus standard-of-care endocrine therapy in patients after at least 2 years of standard adjuvant endocrine therapy, and CAMBRIA-2 (NCT05952557), comparing camizestrant with/without abemaciclib versus standard-of-care endocrine therapy with/without abemaciclib in patients who are starting adjuvant endocrine therapy.

CONCLUSIONS

This phase I study in patients with heavily pre-treated advanced ER+, HER2− breast cancer demonstrates camizestrant's encouraging efficacy, together with a tolerable safety profile. The ongoing subsequent parts of SERENA-1 aim to further investigate camizestrant in combination with other anticancer agents relevant to ER+, HER2− advanced breast cancer, including palbociclib, abemaciclib,[32] everolimus, and capivasertib.[33]

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DISCLOSURE

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DATA SHARING

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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