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CLINICAL TRIAL PROTOCOL

CAMBRIA-1 & CAMBRIA-2 phase III trials: camizestrant versus standard endocrine therapy in ER+/HER2– early breast cancer

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ABSTRACT

Novel selective estrogen receptor degraders (SERDs) are a promising therapeutic option under investigation for patients with estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer. The efficacy of novel SERDs in the treatment of advanced disease has prompted investigation into their use in the early disease setting, to reduce breast cancer recurrence. Here, we describe the design and rationale of the phase III, randomized, open-label CAMBRIA-1 and CAMBRIA-2 studies. CAMBRIA-1 and CAMBRIA-2 are comparing the next-generation oral SERD camizestrant versus standard-of-care endocrine therapy (aromatase inhibitors or tamoxifen) in patients with ER-positive/HER2-negative early breast cancer, who are at intermediate or high risk of disease recurrence. CAMBRIA-1 is comparing 5 years of camizestrant versus endocrine therapy in patients who have already received 2–5 years of standard endocrine therapy, with or without cyclin-dependent kinase 4/6 inhibitors, and are without recurrence. CAMBRIA-2 is comparing 7 years of upfront adjuvant camizestrant versus endocrine therapy, with abemaciclib permitted in both treatment arms for the first 2 years. The primary endpoint for both studies is invasive breast cancer-free survival. Secondary endpoints include invasive disease-free survival, distant recurrence-free survival, overall survival, pharmacokinetics, patient-reported outcomes, safety and tolerability.

Tweetable abstract: CAMBRIA-1 and CAMBRIA-2 are ongoing, randomized, open-label trials of adjuvant camizestrant, either as an upfront treatment or as a treatment after standard endocrine therapy, in patients with HR+/HER2– early breast cancer at intermediate to high risk of disease recurrence.

Clinical Trial Registration: NCT05774951 (CAMBRIA-1); NCT05952557 (CAMBRIA-2).

ARTICLE HISTORY

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KEYWORDS

Breast; clinical trials; drug development; hormonal therapy; women's health

PLAIN LANGUAGE SUMMARY

Why will we perform this study? People with early-stage breast cancer in which the cancer cells have receptors for the hormones estrogen and/or progesterone are typically treated with standard endocrine therapies, which are cancer treatments that remove or block hormones. After surgery, endocrine therapies such as tamoxifen, anastrozole, letrozole or exemestane, are usually given for at least 5 years to prevent the breast cancer from returning and may be given for longer to high-risk patients. While this is currently the recommended treatment, it does not prevent cancer from returning in everyone. Camizestrant is a drug that blocks and degrades estrogen receptors in cancer cells, reducing their growth and spread. Previous research has already shown that camizestrant is more effective at delaying the growth and spread of advanced-stage breast cancer than fulvestrant, a currently approved treatment option for advanced-stage disease. Here, we describe the two CAMBRIA studies, which will test whether camizestrant is more effective than standard endocrine therapy at preventing breast cancer from returning in participants with early-stage disease.

How will we perform this study? In CAMBRIA-1, participants who have completed surgery and have been receiving adjuvant endocrine therapy for 2–5 years will be treated for 5 years with either camizestrant or a continuation of standard endocrine therapy. In CAMBRIA-2, participants who have completed surgery and received little or no prior endocrine therapy will be treated for 7 years with either camizestrant or standard endocrine therapy, with or without abemaciclib. Both studies will assess whether camizestrant increases the length of time participants live without their breast cancer returning. The studies will also assess how long participants live after receiving camizestrant compared with those who receive standard endocrine therapy, and how well participants cope with treatment side effects. The number of participants expected to receive study treatment is approximately 4300 in CAMBRIA-1 and approximately 5500 in CAMBRIA-2.

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Article highlights

Rationale for the CAMBRIA studies

- A significant proportion of patients with estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative early breast cancer remain at intermediate or high risk of recurrence with metastatic disease following adjuvant treatment with standard endocrine therapy (aromatase inhibitors and/or tamoxifen). The risk of distant recurrence and death from breast cancer persists for decades after initial diagnosis, highlighting the urgent need to develop improved treatment options for these patients.
- Novel selective ER degraders (SERDs) capable of both complete ER antagonism and robust ER degradation are under investigation in patients with ER-positive/HER2-negative early breast cancer. These agents have the potential to deliver clinical efficacy superior to standard endocrine therapy by overcoming mechanisms of therapeutic escape.
- Camizestrant is a next-generation SERD and complete ER antagonist. In phase I and II clinical studies, camizestrant, as monotherapy and in combination with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, has demonstrated a well-tolerated, dose-dependent safety profile and encouraging clinical activity in patients with ER-positive/HER2-negative advanced breast cancer.
- The efficacy of camizestrant in the treatment of advanced breast cancer has prompted investigation into its use in the early disease setting, as a strategy to reduce breast cancer recurrence and death due to metastatic disease.

Design of the CAMBRIA studies

- The phase III, randomized, open-label CAMBRIA studies are comparing camizestrant (75 mg once daily) versus standard-of-care endocrine therapy (aromatase inhibitor or tamoxifen) in women and men with ER-positive/HER2-negative early breast cancer.
- CAMBRIA-1 is comparing 5 years of camizestrant versus endocrine therapy in patients who have received 2–5 years of standard endocrine therapy, with or without CDK4/6 inhibitors, without recurrence. Eligible patients must have completed definitive locoregional therapy (surgery ± radiotherapy) ± (neo)adjuvant systemic chemotherapy and be at intermediate or high risk of recurrence. Patients will be randomized 1:1 to continue receiving standard endocrine therapy ± luteinizing hormone-releasing hormone agonist (LHRHa) or camizestrant ± LHRHa.
- CAMBRIA-2 is comparing 7 years of upfront adjuvant camizestrant versus endocrine therapy, with or without adjuvant abemaciclib. Eligible patients must have completed definitive locoregional therapy (surgery ± radiotherapy) ± (neo)adjuvant systemic chemotherapy and be at intermediate – high or high risk of recurrence. Patients will be randomized 1:1 to receive standard endocrine therapy ± LHRHa ± abemaciclib or camizestrant ± LHRHa ± abemaciclib.
- The primary endpoint for both studies is invasive breast cancer-free survival, defined as per STEEP 2.0 criteria. Key secondary endpoints include invasive disease-free survival and distant recurrence-free survival.

Conclusion

- The CAMBRIA-1 and CAMBRIA-2 studies will help to define the role of camizestrant in the early disease setting in two distinct but overlapping populations of patients at intermediate, intermediate – high or high risk of early or late disease recurrence.

1. Introduction

1.1. Current treatment approaches to estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative early breast cancer

In women, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related death, accounting for 666,000 deaths worldwide in 2022 [1]. In high-income countries, most patients (~90%) present with cancer that is confined to the breast and lymph nodes (stages I – III) [2–5], of which 75% have tumors that are hormone receptor (HR)-positive (expressing ER and/or progesterone receptors [PgR]) [6].

For patients with ER-positive/HER2-negative early breast cancer, definitive surgery ± radiotherapy ± chemotherapy, followed by endocrine therapy offers curative potential [7–10]. The addition of abemaciclib (a cyclin-dependent kinase 4/6 [CDK4/6] inhibitor) during the first 2 years of endocrine therapy is a recommended treatment option for certain patients at high risk of disease recurrence [10] and has been shown to improve disease-free survival at 5 years by 7.6% [11]. The addition of ribociclib to adjuvant endocrine therapy has been shown to improve invasive disease-free survival (IDFS) at 3 years by 3.3%, and is also a treatment option for certain patients at high risk of recurrence [12,13]. Mature overall survival (OS) data from trials evaluating the efficacy of abemaciclib and ribociclib in the early breast cancer setting are awaited [11,12]. The addition of adjuvant olaparib (a poly [ADP-ribose] polymerase inhibitor) to endocrine therapy is a recommended treatment option for certain patients with germline *BRCA1/2* gene mutations (gBRCAm) [10], and has been shown to improve OS at 6 years by 4.4% in patients with gBRCAm compared with endocrine therapy alone [14,15].

Standard-of-care adjuvant endocrine therapy options in women include aromatase inhibitors, tamoxifen, or a sequence of both. Choice of endocrine therapy is based on the individual risk of disease recurrence, the presence of comorbidities such as osteoporosis, treatment tolerability, patient preference, and menopausal status [8,10]. In pre- and perimenopausal women, ovarian function suppression (OFS) with either gonadotropin-releasing hormone (GnRH) agonists (also known as luteinizing hormone-releasing hormone agonists; LHRHa), radiation therapy, or bilateral oophorectomy is required with aromatase inhibitor treatment and may be considered in combination with tamoxifen. Whilst the addition of OFS to adjuvant tamoxifen has been shown to improve disease-free survival [16,17], tamoxifen monotherapy remains a valuable treatment option for premenopausal patients with lower-risk disease, considering the effects of treatment on patient quality of life [18]. Combined analysis of the SOFT and TEXT trials reported a significant improvement in disease-free survival in premenopausal patients treated with aromatase inhibitor + OFS compared with those treated with tamoxifen + OFS [19]. This was further supported by a meta-analysis reporting an approximate 3% reduction in the absolute risk of disease recurrence at 5 and 10 years with aromatase inhibitor + OFS compared with tamoxifen + OFS [20]. In postmenopausal patients, aromatase inhibitor therapy has been associated with significantly longer disease-free survival and time to distant recurrence [21], as well as a lower 10-year breast cancer mortality rate and risk of endometrial cancer, compared with tamoxifen [22]. Nevertheless, the use of adjuvant tamoxifen offers a balance between efficacy and toxicity for some women, due to the increased risk of bone fractures associated with longer durations of aromatase inhibitor treatment [20,23]. Options for adjuvant endocrine therapy in men include tamoxifen or, if tamoxifen is contraindicated, an aromatase inhibitor combined with a GnRH analog [10].

The recommended duration of endocrine therapy is dependent on risk factors, including tumor stage, tumor biology, and menopausal status [7–9]. Whilst 5 years of endocrine therapy may be adequate for stage I, lymph node-negative breast tumors, a significant proportion of patients with nodal involvement remain at intermediate or high risk of recurrence with metastatic disease

after 5 years of therapy (Figure 1) [24], and may be offered extended adjuvant endocrine therapy for up to 10 years [7–9]. For patients who are premenopausal at diagnosis, clinical practice guidelines recommend either 5 years of adjuvant aromatase inhibitor + OFS followed by a further 3–5 years of aromatase inhibitor, or 5 years of tamoxifen ± OFS followed by aromatase inhibitor or tamoxifen for 5 years or no further endocrine therapy, depending on menopausal status and risk of recurrence [9,10]. For patients who are postmenopausal at diagnosis, guidelines recommend an initial 2–5 years of aromatase inhibitor, which may be either extended to up to 10 years or followed by tamoxifen to a total of 5 years of endocrine therapy, depending on the patient's risk profile. An alternative recommended option comprises an initial 2–6 years of tamoxifen, which may then either be extended to a maximum of 10 years or followed by up to 5 years of aromatase inhibitor [8–10]. In postmenopausal women, extension of endocrine therapy to 10 years with the aromatase inhibitor anastrozole was reported to offer no benefit over extension to 7 years [25], and 7–8 years of endocrine therapy is widely considered optimal for most high-risk patients [9,25,26].

For patients with stage II – III early breast cancer, the risk of recurrence with metastatic disease following standard-of-care endocrine therapy has been shown to persist for up to 32 years [24,27]. Patients with four to nine positive nodes at diagnosis have a reported 52% risk of distant recurrence and 49% risk of death from breast cancer within 20 years of standard-of-care endocrine therapy [24]. The persistent risk of disease recurrence and the associated negative impact on patient long-term mental health [28] demonstrates a clear and urgent need to develop improved treatment options for patients with HR-positive, early-stage breast cancer with higher risk of recurrence.

1.2. The role of selective ER degraders (SERDs) in the treatment of early breast cancer

SERDs bind to the ligand-binding domain of ER alpha, antagonize estrogen binding and induce proteasome-mediated degradation of the receptor [29]. This provides an alternative endocrine therapy option with a distinct mechanism of action from aromatase inhibitors and selective ER modulators (SERMs) such as tamoxifen. Whilst there are currently no clinical trial data to support use of SERDs as adjuvant endocrine therapy in early breast cancer, and no approvals to date, fulvestrant was approved as a treatment for advanced breast cancer in 2002 and has shown superior efficacy compared with anastrozole as a first-line treatment in postmenopausal patients with endocrine therapy-naïve advanced disease [30,31]. However, maximal ER inhibition is not achieved with fulvestrant [32–34] and administration via monthly intramuscular injections can be uncomfortable and burdensome for patients [35,36].

Molecular responses to short-term neoadjuvant endocrine therapy can be predictive of clinical response in the adjuvant setting [37]. In patients with HR-positive/HER2-negative early breast cancer, pre-surgical window-of-opportunity studies have demonstrated the ability of SERDs to reduce tumor ER and/or PgR scores [34,38], suppress the expression of key ER target genes [38], and decrease levels of the proliferation marker Ki67 [34,38]. A potent, next-generation SERD (ngSERD) capable of greater target engagement than fulvestrant has therefore been hypothesized to deliver clinical efficacy superior to standard-of-care endocrine therapy in the adjuvant setting [34], with a potential for improved tolerability owing to the distinct mechanism of action compared to aromatase inhibitors and tamoxifen.

1.3. Camizestrant in ER-positive/HER2-negative breast cancer

Camizestrant is a ngSERD and complete ER antagonist (Figure 2) that was designed to improve on fulvestrant and first-generation oral SERDs [39]. In preclinical studies, camizestrant demonstrated complete ER antagonism, robust and selective ER degradation, and significant antiproliferative activity in models of ER-driven breast cancer with either wild-type or mutant estrogen receptor-1 genes (*ESR1*) [40]. In patient-

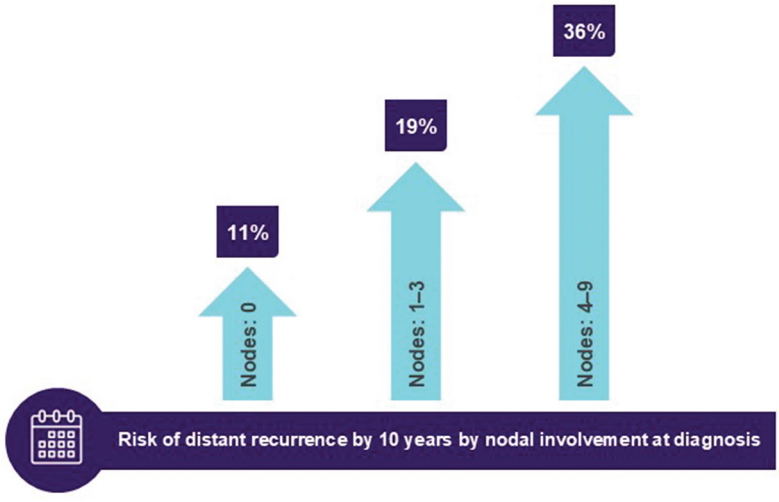

Figure 1. Distant recurrence in women with ER+ early breast cancer who were scheduled to receive 5 years of adjuvant endocrine therapy [24].

Data from 74,194 women with ER+ breast cancer and T1 or T2 disease enrolled in 78 trials at year 0 and scheduled to receive 5 years of adjuvant endocrine therapy and then discontinue therapy. Risk of distant recurrence by nodal involvement at diagnosis is shown: no nodal involvement, 1–3 nodes, 4–9 nodes. ER+: Estrogen receptor-positive.

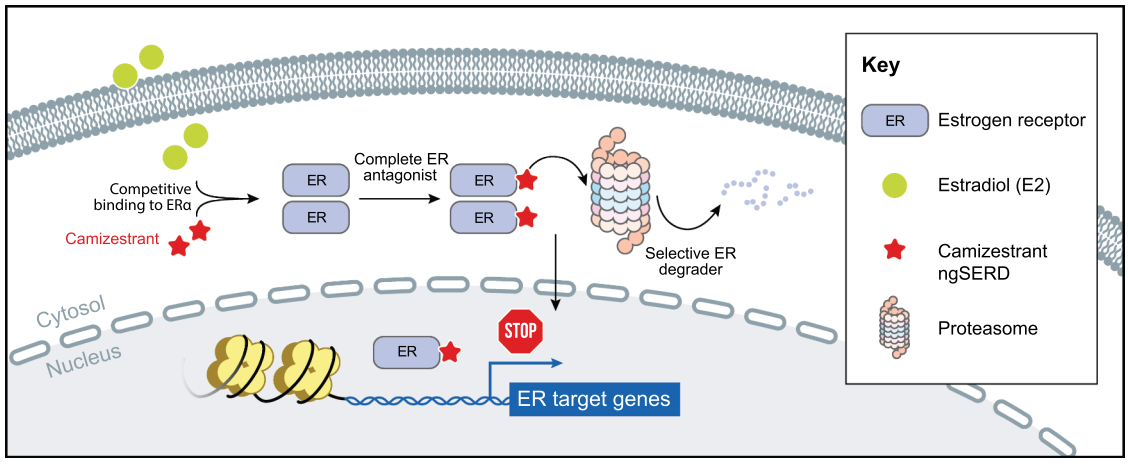

Figure 2. Camizestrant mechanism of action.

ER: Estrogen receptor; ngSERD: Next-generation selective estrogen receptor degrader.

derived xenograft models, camizestrant showed enhanced efficacy compared with fulvestrant [40].

Camizestrant has demonstrated a well-tolerated, dose-dependent safety profile and encouraging clinical activity in patients with ER-positive/HER2-negative advanced breast cancer in studies conducted as part of the SERENA clinical trial program [41–45]. In the phase I SERENA-1 trial, pharmacokinetics data confirmed the suitability of camizestrant for once-daily (QD) dosing and showed encouraging efficacy as monotherapy [45] and in combination with the standard-of care-agents abemaciclib, palbociclib, and ribociclib [41–43,46], as well as with the pan-AKT inhibitor capivasertib [44]. In the randomized phase II SERENA-2 trial, camizestrant demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) versus fulvestrant regardless of dose (75 mg or 150 mg) in postmenopausal women with disease recurrence or progression on one or more lines of endocrine therapy. Median PFS was 7.2 months with 75 mg camizestrant versus 3.7 months with fulvestrant (adjusted hazard ratio 0.58 [90% confidence interval (CI) 0.41, 0.81]), and 7.7 months with 150 mg camizestrant (adjusted hazard ratio vs fulvestrant 0.67 [90% CI 0.48, 0.92]) [47]. PFS with 75 mg camizestrant was consistent in patients with and without detectable *ESR1* mutations [47]. In the phase II, pre-surgical, window-of-opportunity SERENA-3 study, the biological effects of three different camizestrant doses (75 mg, 150 mg, and 300 mg) were evaluated in postmenopausal women with ER-positive/HER2-negative early breast cancer. Camizestrant reduced ER expression by approximately 65% irrespective of dose or treatment duration, and reduced Ki67 score by approximately 82% within 15 days of treatment, irrespective of dose. Together, SERENA-2 and SERENA-3 demonstrated that 75 mg camizestrant achieved maximal efficacy, supporting 75 mg QD as the optimal and recommended camizestrant dose [48].

Ongoing phase III trials are now evaluating camizestrant plus CDK4/6 inhibitors in ER-positive/HER2-negative advanced breast cancer. SERENA-4 (NCT04711252) is evaluating the safety and efficacy of camizestrant + palbociclib versus anastrozole + palbociclib in patients who have not received any previous systemic treatment for their locoregionally recurrent or metastatic disease. SERENA-6 (NCT04964934) is evaluating the safety and efficacy of switching from aromatase inhibitors (letrozole or anastrozole) to camizestrant, whilst maintaining the same CDK4/6 inhibitor partner (palbociclib, abemaciclib, or ribociclib), in patients with *ESR1* mutations detectable in circulating tumor DNA [29].

The efficacy of camizestrant, as well as other novel SERDs, in the treatment of advanced breast cancer has prompted investigation into their use in the early disease setting, as a strategy to reduce breast cancer recurrence and death due to metastatic disease. Several ongoing clinical studies are evaluating novel oral SERDs in the adjuvant setting in early-stage breast cancer, including camizestrant (CAMBRIA-1 and CAMBRIA-2, described here), giredestrant [49,50], and imlunestrant [51,52]; results of these studies are awaited.

1.4. The potential of camizestrant to reduce the risk of recurrence in ER-positive/HER2-negative early breast cancer

The CAMBRIA studies are investigating the potential of camizestrant to reduce the risk of recurrence in patients with ER-positive/HER2-negative early breast cancer, compared with standard endocrine therapy. CAMBRIA-1 (NCT05774951) is evaluating the benefit of 5 years of camizestrant treatment in patients with an intermediate or high risk of recurrence who have completed definitive locoregional therapy and received 2–5 years of standard endocrine therapy for ER-positive/HER2-negative early breast cancer without disease recurrence. CAMBRIA-2 (NCT05952557) is examining the benefit of 7 years of upfront adjuvant camizestrant in patients with ER-positive/HER2-negative early breast cancer at intermediate – high or high risk of disease recurrence.

Abemaciclib will be permitted in both treatment arms in CAMBRIA-2 according to local practice and availability, and prior treatment with CDK4/6 inhibitor and olaparib is permitted in CAMBRIA-1.

2. Study designs

Descriptions of the CAMBRIA-1 and CAMBRIA-2 study designs are based on CAMBRIA-1 clinical study protocol version 4.0 (11 March 2024) and CAMBRIA-2 clinical study protocol version 3.0 (20 May 2024).

2.1. Objectives

The primary objective of CAMBRIA-1 is to demonstrate the superiority of camizestrant compared with standard endocrine therapy by assessment of invasive breast cancer-free survival (IBCFS) in patients who have already received 2–5 years of standard endocrine therapy, with or without CDK4/6 inhibitors, and are without recurrence. The primary objective of CAMBRIA-2 is to demonstrate the superiority of camizestrant versus standard endocrine therapy, with or without adjuvant abemaciclib, by assessment of IBCFS.

2.2. Study designs

CAMBRIA-1 is a phase III randomized, open-label study that aims to assess the efficacy and safety of extended adjuvant therapy with camizestrant versus standard endocrine therapy in patients with ER-positive/HER2-negative early breast cancer. Patients will be randomized 1:1 to continue receiving standard endocrine therapy of the investigator's choice (tamoxifen or aromatase inhibitor) ± LHRHa or camizestrant ± LHRHa (Figure 3).

CAMBRIA-2 is a phase III, randomized, open-label study that aims to assess the efficacy and safety of upfront camizestrant versus standard endocrine therapy in patients with ER-positive /HER2-negative early breast cancer. Patients will be randomized 1:1 to receive standard endocrine therapy of the investigator's choice (tamoxifen or aromatase inhibitor) ± LHRHa ± abemaciclib or camizestrant ± LHRHa ± abemaciclib (Figure 4).

2.3. Study treatments

In both studies patients will be centrally assigned to randomized study treatment using an interactive voice/web response system. In both studies, the control arm is standard endocrine therapy of the investigator's choice: tamoxifen (20 mg QD) or aromatase inhibitor (exemestane 25 mg, letrozole 2.5 mg, or anastrozole 1 mg QD). Patients randomized to the standard endocrine therapy arm may switch from one endocrine therapy to another if clinically indicated during the study. The dose of camizestrant in both studies is 75 mg QD, and dose reductions will not be permitted.

In CAMBRIA-1, pre- and perimenopausal female patients, and male patients, must receive an LHRHa if receiving camizestrant. Pre- and perimenopausal female patients, and male patients receiving standard-of-care treatment with aromatase inhibitors or tamoxifen will receive LHRHa as medically applicable. In CAMBRIA-2, pre- and perimenopausal female patients in both treatment arms, and male patients receiving camizestrant or aromatase inhibitors must receive an LHRHa. LHRHa in both studies will be goserelin, leuprorelin, or triptorelin, and will be administered as monthly or 3-monthly injections per investigator's discretion.

Treatment for 60 months in CAMBRIA-1 and 84 months in CAMBRIA-2 will enable a total duration of endocrine therapy (including endocrine therapy prior to enrollment) of up to approximately 10 years and 7 years, respectively. This is in line with current literature indicating extended endocrine therapy beyond 5 years, i.e., the current standard of care, may reduce risk of recurrence in higher-risk patients [25,53]. In both studies, randomized patients will receive study treatment until an IBCFS event, completion of the defined treatment period, patient withdrawal of consent, initiation of subsequent anti-cancer therapy or investigator determination that the patient is no longer benefiting from study treatment.

2.4. Eligibility criteria

For both studies, eligible patients (Table 1) are women (pre-, post-, and perimenopausal) and men aged ≥18 years with histologically confirmed ER-positive/HER2-negative early-stage resected breast cancer with absence of advanced disease (ER-positivity defined as ER expression in > 10% of tumor cells; HER2-negativity defined as 0 or 1+ intensity on immunohistochemical [IHC] testing or no amplification on in situ hybridization). In CAMBRIA-1, patients must have completed definitive locoregional therapy (surgery ± radiotherapy) ± (neo)adjuvant systemic chemotherapy and be at intermediate or high risk of recurrence, as defined in the protocol. Patients must be receiving standard adjuvant endocrine therapy for ≥ 2 and ≤5 years (+3 months) with at least 5 years of remaining adjuvant endocrine therapy planned. In CAMBRIA-2, patients must have completed definitive locoregional therapy (surgery ± radiotherapy) ± (neo)adjuvant systemic chemotherapy and be at intermediate – high or high risk of recurrence, as defined in the protocol.

Key exclusion criteria across both studies include inoperable locally advanced breast cancer, or distant metastatic disease, pathological complete response following neoadjuvant therapy, specified prior or concomitant therapy (including previous treatment with camizestrant, investigational SERDs or investigational endocrine agents [CAMBRIA-1]/investigational ER-targeting agents [CAMBRIA-2]) or fulvestrant, prior breast cancer, specified previous cancers, and specified cardiac symptoms or abnormalities.

2.5. Planned sample sizes

The number of patients randomized to receive study treatment will be approximately 4300 in CAMBRIA-1 and approximately 5500 in CAMBRIA-2.

2.6. Study procedures

In both studies, disease recurrence assessments will be performed at months 4 and 7, followed by every 6 months thereafter up to 60 months (CAMBRIA-1) or 84 months (CAMBRIA-2) (regardless of treatment discontinuation), and then every 12 months (or when clinically indicated) until distant disease recurrence, death, or end of study. Patients who have discontinued study treatment prior to distant recurrence, regardless of whether or not they have commenced subsequent anti-cancer therapy, will be

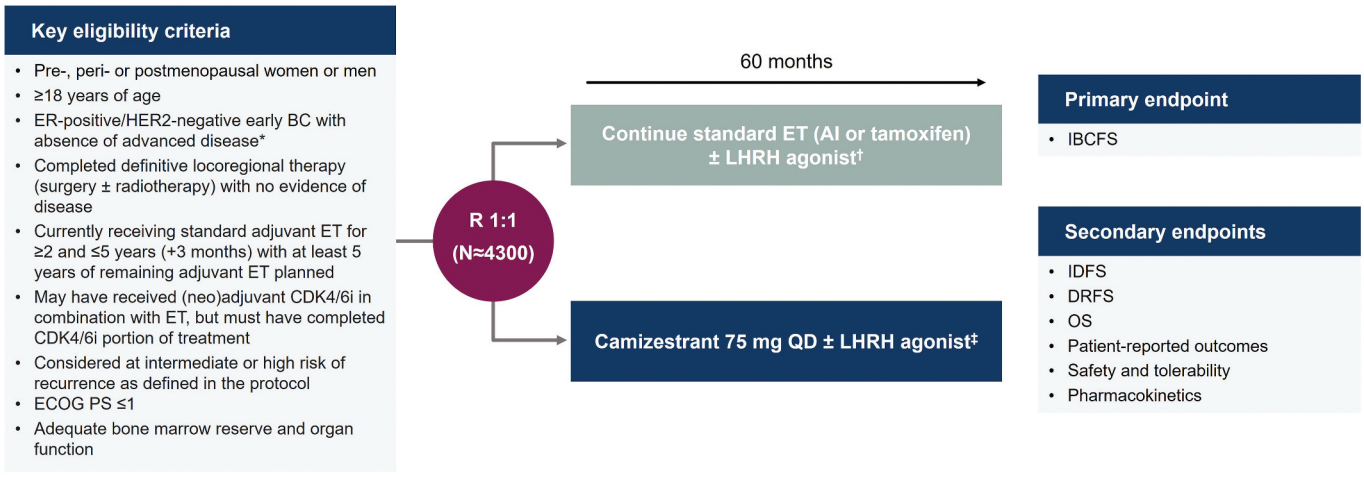

Figure 3. CAMBRIA-1 trial schema.

The CAMBRIA-1 study design presented aligns with clinical study protocol global amendment 3 v4.0 (11 March 2024).

*ER+: ER expression in > 10% of tumor cells; HER2–: IHC 0 or 1-positive and negative by ISH; †Investigator's choice: AI (exemestane, letrozole, anastrozole) or tamoxifen, standard dose per investigator, once daily. Pre- and perimenopausal women, and men, will be administered an LHRHa per local guidelines; ‡Pre- and perimenopausal women, and men, receiving camizestrant must be administered an LHRHa.

AI: Aromatase inhibitor; BC: Breast cancer; CDK4/6i: Cyclin-dependent kinase 4/6 inhibitor; DRFS: Distant relapse-free survival; ECOG PS: Eastern Cooperative Oncology Group performance status; ER: Estrogen receptor; ET: Endocrine therapy; HER2: Human epidermal growth factor receptor 2; IBCFS: Invasive breast cancer-free survival; IDFS: Invasive disease-free survival; IHC: Immunohistochemistry; ISH: in situ hybridization; LHRH(a): Luteinizing hormone-releasing hormone (agonist); OS: Overall survival; QD: Once daily; R: Randomized.

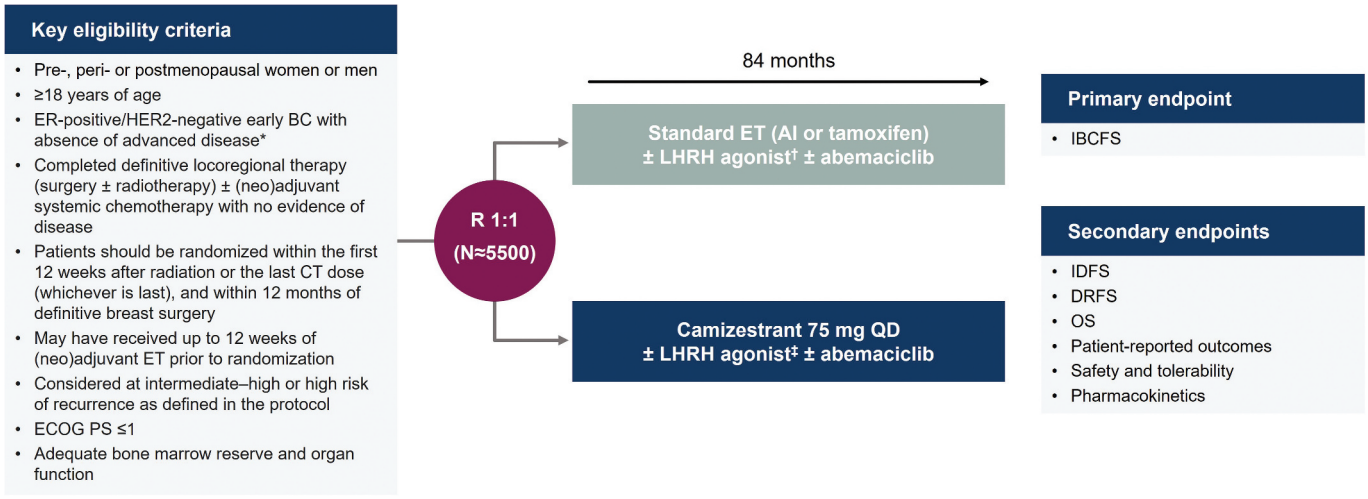

Figure 4. CAMBRIA-2 trial schema.

The CAMBRIA-2 study design presented aligns with clinical study protocol global amendment 1 v3 (20 May 2024).

*ER+: ER expression in > 10% of tumor cells; HER2–: IHC 0 or 1-positive and negative by ISH; †Investigator's choice: AI (exemestane, letrozole, anastrozole) or tamoxifen, standard dose per investigator, once daily. Pre- and perimenopausal female patients in both treatment arms will be administered an LHRHa. Male patients will be administered an LHRHa if receiving AI. ‡Pre- and perimenopausal women, and men, receiving camizestrant must be administered an LHRHa.

AI: Aromatase inhibitor; BC: Breast cancer; CDK4/6i: Cyclin-dependent kinase 4/6 inhibitor; CT: Chemotherapy; DRFS: Distant relapse-free survival; ECOG PS: Eastern Cooperative Oncology Group performance status; ER: Estrogen receptor; ET: Endocrine therapy; HER2: Human epidermal growth factor receptor 2; IBCFS: Invasive breast cancer-free survival; IDFS: Invasive disease-free survival; IHC: Immunohistochemistry; ISH: In situ hybridization; LHRH(a): Luteinizing hormone-releasing hormone (agonist); OS: Overall survival; QD: Once daily; R: Randomized.

followed up with disease recurrence assessments unless they have withdrawn all consent to study-related assessments. Disease recurrence events to be assessed by the local investigator include ipsilateral breast and other locoregional invasive breast cancer events, invasive contralateral breast cancer, distant recurrence and death (attributable to any cause). Second primary non-breast invasive cancer will also be assessed. Patient-reported outcome measurements in CAMBRIA-1 and CAMBRIA-2 will include several clinical outcome assessment tools to help inform the overall benefitrisk profile of treatment in this setting. In both studies, pre-dose whole blood samples will be collected for pharmacokinetics analysis from a subset of the study population. Adverse events will be monitored at every visit or via phone or video call outside of the visiting schedule throughout the study and during the safety follow-up period of 28 days (+7 days) following last dose of study treatment. An independent data monitoring committee will review unblinded safety data and interim efficacy data and make recommendations on continuing the study

Table 1. Summary of inclusion and exclusion criteria.

Inclusion criteria		
	CAMBRIA-1	CAMBRIA-2
Sex	Female, male	
Age	≥18 years*	
Menopausal status (female patients only)	Pre-, peri-, or postmenopausal	
Disease characteristics		
Hormone receptor status	Histologically confirmed ER-positive status (ER-positive defined as ER expression in > 10% of tumor cells)	
HER2 status	Histologically confirmed HER2-negative status (HER2-negative defined as immunohistochemistry 0, or 1+, or in situ hybridization negative)	
Disease stage	Early-stage resected invasive breast cancer with absence of advanced disease	
Prior treatment and duration		
Locoregional and systemic therapy	Completed definitive locoregional therapy (surgery ± radiotherapy) ± (neo)adjuvant systemic chemotherapy[†]	
Endocrine therapy	Currently receiving standard adjuvant endocrine therapy for ≥ 2 and ≤5 years (+3 months) at the time of randomization, with at least 5 years of remaining adjuvant endocrine therapy planned	Patients may have received up to 12 weeks of (neo)adjuvant endocrine therapy prior to randomization
CDK4/6 inhibitor	Patients may have received a CDK4/6 inhibitor plus endocrine therapy but must have completed CDK4/6 treatment prior to study initiation	Patients may have received up to 12 weeks of prior abemaciclib
Risk of recurrence	Intermediate or high risk[†]	Intermediate – high or high risk[‡]
ECOG PS	≤1	
Bone marrow reserve/organ function	Adequate bone marrow reserve and organ function	
Exclusion criteria		
Medical conditions	Patients with inoperable locally advanced breast cancer, or distant metastatic (including contralateral axillary lymph nodes) disease	
	Patients with pathological complete response following treatment with neoadjuvant therapy	
	History of another cancer (except non-melanoma skin cancer or carcinoma in situ of the cervix or considered a very low risk of recurrence per investigator judgment, unless in complete remission with no therapy for a minimum of 5 years from the date of randomization)	
	History of previous breast cancer (except ipsilateral DCIS treated by locoregional therapy alone ≥5 years ago or contralateral DCIS treated with locoregional therapy at any time); patients with DCIS treated with endocrine therapy must have completed endocrine therapy ≥5 years prior to the diagnosis of invasive breast cancer	History of previous breast cancer (except ipsilateral DCIS treated by locoregional therapy alone ≥5 years ago or contralateral DCIS treated with locoregional therapy at any time); patients with DCIS treated with endocrine therapy must have completed endocrine therapy ≥5 years prior to randomization
	Severe or uncontrolled systemic diseases	
	Chronic gastrointestinal disease, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption, distribution, metabolism, or excretion of study treatment	
	Specified cardiac symptoms or abnormalities	
Prior/concomitant therapy	Major surgical procedure or significant traumatic injury within 2 weeks of randomization	
	Previous treatment with camizestrant, investigational SERDs/investigational endocrine agents or fulvestrant	Previous treatment with camizestrant, investigational SERDs/investigational ER targeting agents or fulvestrant
Other	Documented hypersensitivity to active or inactive excipients of camizestrant or drugs with a similar chemical structure or class to camizestrant, known hypersensitivity to LHRHa or any of its excipients that would preclude the patient from receiving LHRHa (in pre-/perimenopausal female and male patients) or undiagnosed vaginal bleeding (in female patients receiving LHRH)	
	Pregnant or breastfeeding female patients	

*Or per national guidelines; [†]Patients should be randomized within the first 12 weeks after radiation or the last CT dose (whichever is later), and within 12 months of definitive breast surgery; [‡]Defined in line with protocol.
CDK4/6i: Cyclin-dependent kinase 4/6 inhibitor; CT: Chemotherapy; DCIS: Ductal carcinoma in situ; ECOG PS: Eastern Cooperative Oncology Group performance status; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; LHRH(a): Luteinizing hormone-releasing hormone (agonist); SERD: Selective estrogen receptor degrader.

based on their analysis. Compliance with the study intervention will be assessed and documented at each study assessment for patients self-administering study treatment at home by counting the number of returned capsules and by direct questioning. Additionally, all patients will be requested to complete a monthly Treatment Adherence Diary. All patients will undergo an end-of-treatment visit and follow-up visits will be carried out every 12 months from the safety follow-up visit for assessment of survival up until the end of the study. Following completion of the study treatment period, patients will be treated in accordance with local practice guidelines.

2.7. Endpoints

The primary endpoint for both studies is IBCFS. Key secondary endpoints include IDFS and distant recurrence-free survival (DRFS). Clinical efficacy endpoints (IBCFS, IDFS, DRFS) are defined as per Standardized Definitions for Efficacy End Points (STEEP) 2.0 criteria [54]. Other secondary endpoints include OS, patient-reported outcomes, and pharmacokinetics. Safety and tolerability will be evaluated in terms of type, incidence, severity (as graded by National Cancer Institute-Common Terminology Criteria for Adverse Events v5.0), seriousness and relationship of adverse events to study treatments (Table 2).

2.8. Statistical analyses

The primary analysis of IBCFS will be conducted using stratified log-rank test adjusting for study-specific stratification factors. Descriptive statistics will be used to present safety data.

2.9. Ethical considerations

The protocols, any protocol amendments, and all other relevant documents for the multicenter CAMBRIA-1 and CAMBRIA-2 studies were approved by an institutional review board or independent ethics committee at each participating institution before the studies were initiated. Both studies are being conducted in accordance with consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable good clinical practice guidelines, and all applicable local laws and regulations. Efforts will be made to ensure equality, diversity, and inclusion during patient recruitment and written, informed consent will be obtained from all patients by the investigator or suitably trained representative prior to initiation of study procedures.

2.10. Participating institutions

In CAMBRIA-1 and CAMBRIA-2, patients will be randomized at 682 study sites in 39 countries and 700 sites in 43 countries, respectively (Figure 5). All participating sites are listed on ClinicalTrials.gov.

3. Conclusions

A significant proportion of patients with ER-positive/HER2-negative early breast cancer are considered to have an intermediate/intermediate – high or high risk of recurrence with incurable disease following standard-of-care endocrine therapy, with the risk of recurrence persisting for decades after the initial diagnosis. New endocrine therapy options with greater clinical efficacy are required to address this unmet need. Camizestrant is a ngSERD and complete ER antagonist that has demonstrated encouraging clinical activity in the advanced disease setting, as well as clinical pharmacodynamic activity in the preoperative setting, and has the potential to improve on current standard-of-care endocrine therapy in early breast cancer. The CAMBRIA-1 and CAMBRIA-2 studies will help to define the role of camizestrant in the early disease setting, in two distinct but overlapping populations of patients at intermediate/intermediate – high or high risk of either early or late disease recurrence. The studies aim to address the clinical unmet need in these populations by reducing the risk of recurrence and death due to metastatic disease.

Table 2. Study endpoints used in CAMBRIA-1 and CAMBRIA-2.

Endpoint		Definition
Primary	IBCFS	Time from randomization to the date of the first occurrence of invasive IBTR, locoregional invasive breast cancer recurrence, distant recurrence, invasive contralateral breast cancer, or death due to any cause (second primary non-breast invasive cancers are excluded)
Secondary	IDFS	Time from randomization to the date of the first occurrence of invasive IBTR, locoregional invasive breast cancer recurrence, distant recurrence, invasive contralateral breast cancer, second primary non-breast invasive cancer, or death due to any cause
	DRFS	Time from randomization to the date of first distant recurrence or death from any cause
	OS	Time from randomization until death from any cause
	Patient-reported outcomes	As evaluated using selected EORTC instruments, Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events, Patients' Global Impression of Treatment Tolerability and Patients' Global Impression of Severity instruments
Safety and tolerability		Safety and tolerability will be evaluated in terms of type, incidence, severity (as graded by NCI-CTCAE v5.0), seriousness, and relationship to study treatments of AEs, vital signs, clinical laboratory results, ECG recordings, and ophthalmological assessments
Additional analyses		Pharmacokinetics

Clinical efficacy endpoints (IBCFS, IDFS, DRFS) are defined as per STEEP 2.0 criteria [54].

AE: Adverse event; DRFS: Distant relapse-free survival; ECG: Electrocardiogram; EORTC: European Organisation for Research and Treatment of Cancer; IBCFS: Invasive breast cancer-free survival; IBTR: Ipsilateral breast tumor recurrence; IDFS: Invasive disease-free survival; NCI-CTCAE v5.0: National Cancer Institute – Common Terminology Criteria for Adverse Events version 5.0; OS: Overall survival; R: Randomized; QD: Once daily.

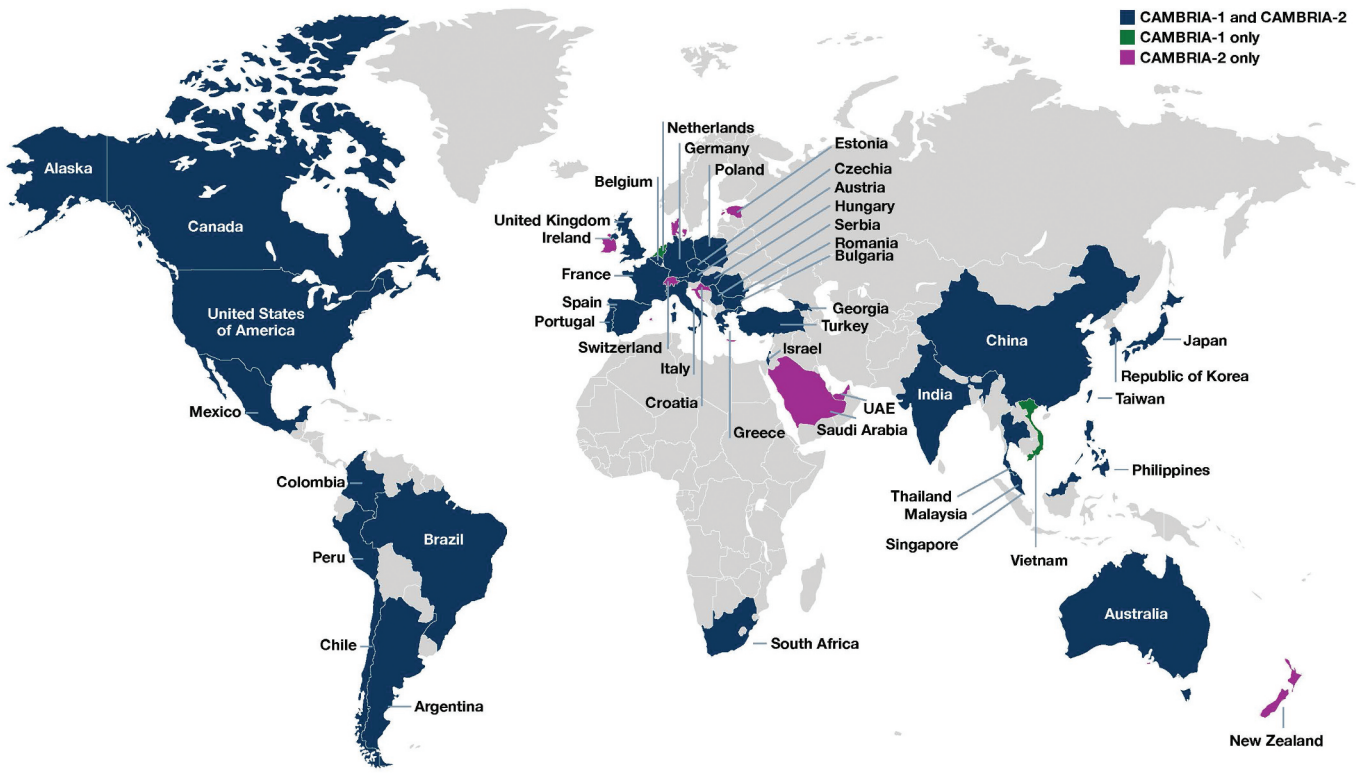

Figure 5. Participating locations in CAMBRIA-1 and CAMBRIA-2.

Acknowledgments

The trial design of CAMBRIA-1 has previously been presented at the European Society for Medical Oncology Congress 2023 (abstract 354TiP) and the San Antonio Breast Cancer Symposium 2023 (abstract PO2-18-09). The trial design of CAMBRIA-2 has previously been presented at the San Antonio Breast Cancer Symposium 2023 (abstract PO4-27-07).

Author contributions

All authors met the criteria for authorship set forth by the International Committee of Medical Journal Editors. Erika P Hamilton, Sibylle Loibl, Thomas Bachelot, Michael Gnant, Naoki Niikura, Yeon Hee Park, Sara M Tolaney, Barbara Pistilli, Priya Rastogi, Kamal S Saini, Ioanna Gioni, Simon Johnston, Raquel Nunes, Angela Quintana, Mary Stuart, Emilia Syta, Andrew Walding, Teresa Klinowska and Ingrid A Mayer were involved in the conception, preparation, and approval of the manuscript.

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Ethical declaration

The protocols, any protocol amendments, and all other relevant documents for the multicenter CAMBRIA-1 and CAMBRIA-2 studies were approved by an institutional review board or independent ethics committee at each participating institution before the studies were initiated. Written, informed consent will be obtained from all patients prior to initiation of study procedures.

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Data availability statement

Study data may be obtained upon request in accordance with AstraZeneca's data-sharing policy, described at: https://www.astrazenecaclinicaltrials.com/our-transparency-commitments/.

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