

VERITAC-2: a global, randomized phase 3 study of ARV-471, a PROteolysis Targeting Chimera (PROTAC) estrogen receptor (ER) degrader, vs fulvestrant in ER+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer

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Objective

- The phase 3 VERITAC-2 study (NCT05654623) will compare the efficacy and safety of vepdegestrant (ARV-471) with the selective ER degrader (SERD) fulvestrant in patients with ER+/HER2- advanced breast cancer after prior combination cyclin-dependent kinase (CDK)4/6 inhibitor therapy and endocrine therapy

References

1. Flanagan JJ, et al. Presented at: SABCS; Dec 4-8, 2018; San Antonio, TX, USA. Poster P5-04-18.
2. Harker AB, et al. *Cancer Cell*. 2020;37(4):496-513.
3. Nathan MR, et al. *Oncol Ther*. 2017;5(1):17-29.
4. Kuter I, et al. *Breast Cancer Res Treat*. 2012;133(1):237-246.
5. Robertson JFR, et al. *Breast Cancer Res*. 2013;15(2):R18.
6. Hurvitz SA, et al. Presented at: SABCS; Dec 6-10, 2022; San Antonio, TX, USA. Oral presentation GS3-03.

Disclosure

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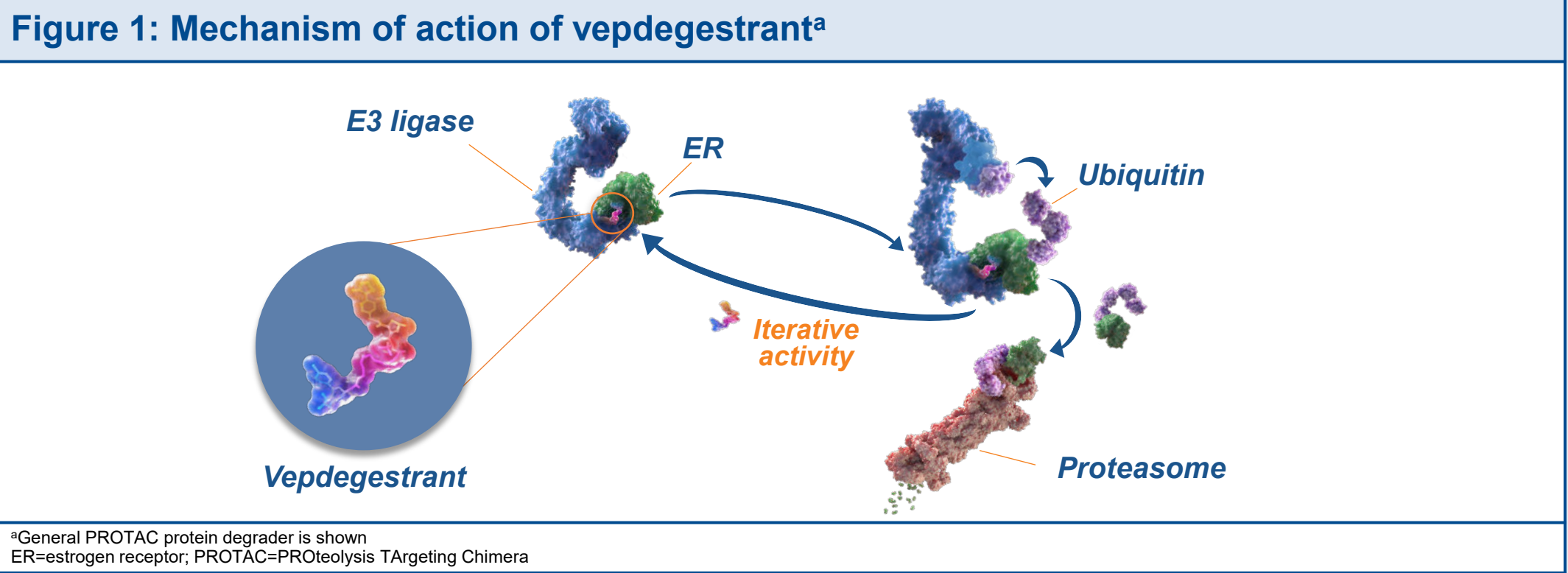


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Background and Rationale

- Vepdegestrant (ARV-471) is an oral PROTAC ER degrader that binds to and degrades wild-type ER and clinically relevant mutants¹
- Vepdegestrant directly binds the cereblon E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation (**Figure 1**), whereas SERDs indirectly recruit the ubiquitin-proteasome system, secondary to conformational changes and/or immobilization of ER²



Study Design

- In this open-label, global, multicenter, phase 3 study, patients are randomized 1:1 to receive vepdegestrant or fulvestrant in 28-day cycles (**Figure 2**)
- Eligible patients have ER+/HER2- advanced breast cancer and prior treatment with a CDK4/6 inhibitor therapy in combination with endocrine therapy (**Table 1**)
- Outcome measures are shown in **Table 2**
- Enrollment is ongoing
- Countries with currently open and planned study sites are shown in **Figure 3**

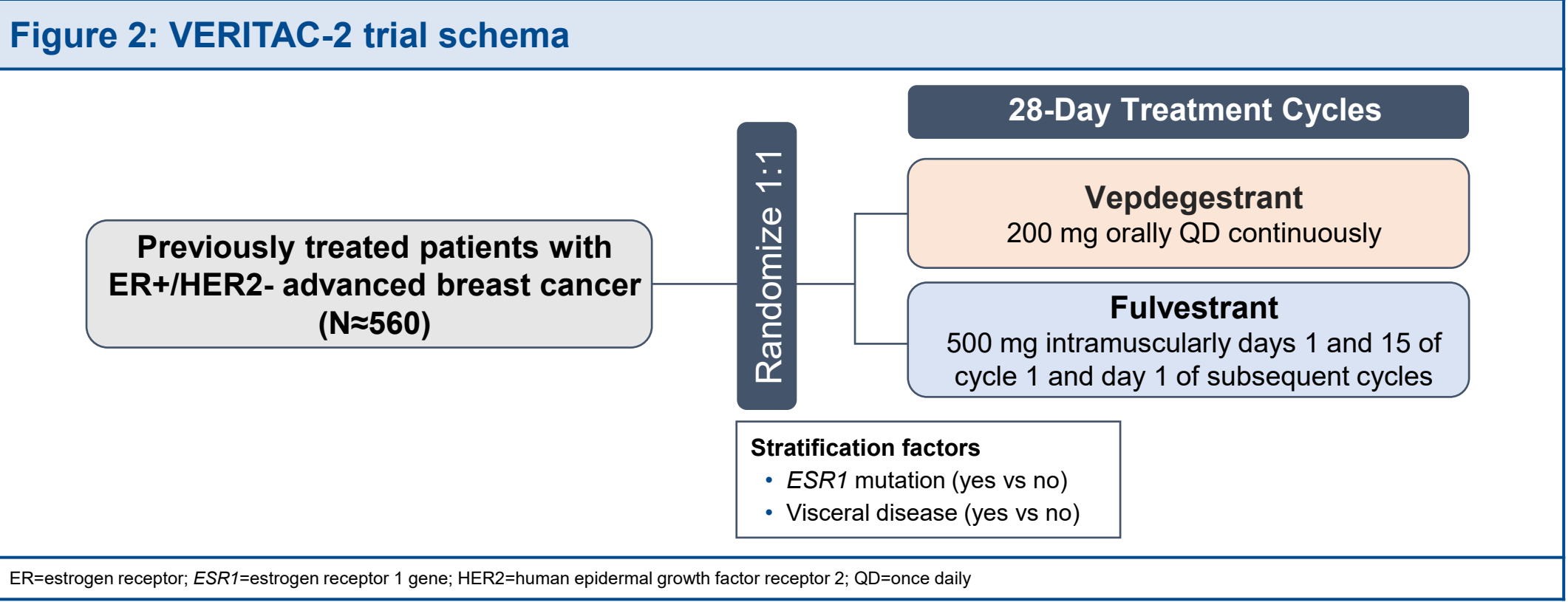
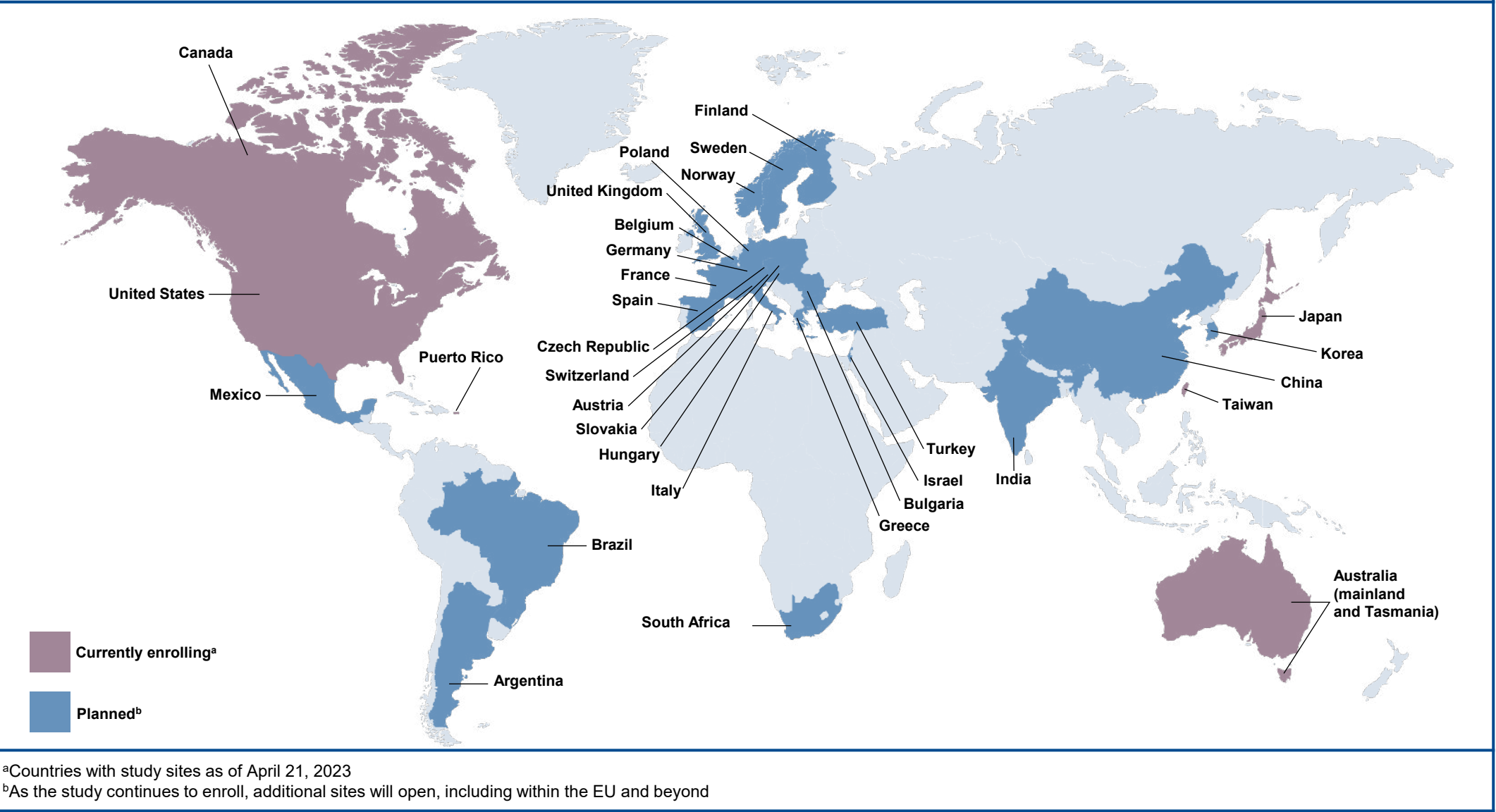


Figure 3: VERITAC-2 study sites



- The SERD fulvestrant must be administered intramuscularly,³ and at its optimal dose, ER protein degradation is limited to only 40%–50%^{4,5}
- In breast cancer xenograft models, vepdegestrant treatment provided substantially greater ER degradation and tumor growth inhibition compared with fulvestrant¹
- In VERITAC, the phase 2 expansion cohort of a first-in-human phase 1/2 study (NCT04072952), vepdegestrant monotherapy showed clinical activity and was well tolerated in heavily pretreated patients with ER+/HER2- advanced breast cancer⁶
 - Clinical benefit rate (CBR)^a was 37.1% (95% CI: 21.5–55.1) and 38.9% (95% CI: 23.1–56.5) in the 200-mg (n=35) and 500-mg (n=36) oral, once-daily (QD) cohorts, respectively
 - Clinical activity was also observed in the mutant *ESR1* subgroup: CBR was 47.4% (95% CI: 24.4–71.1) and 54.5% (95% CI: 32.2–75.6) in the 200-mg (n=19) and 500-mg (n=22) QD cohorts, respectively
 - Most adverse events (AEs) were grade 1/2, with few AEs leading to dose reduction (500 mg, n=3) or discontinuation (200 mg, n=1; 500 mg, n=2)
 - In a subset of patients who received 200 mg QD across the phase 1/2 study (n=9), up to 95% ER degradation was observed, with a median (range) of 69% (28%–95%)
- The phase 3 monotherapy dose (200 mg QD) for the current study was chosen based on comparable efficacy and favorable tolerability relative to 500 mg QD, and robust ER degradation

^aRate of confirmed complete response, partial response, or stable disease ≥24 weeks; evaluable patients were enrolled ≥24 weeks prior to the data cutoff

Table 1: VERITAC-2 key eligibility criteria	
Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none">Women or men aged ≥18 yearsConfirmed ER+/HER2- locoregional recurrent or metastatic breast cancerPrior therapies for locoregional recurrent or metastatic disease must fulfill all the following criteria:<ul style="list-style-type: none">1 line of CDK4/6 inhibitor therapy in combination with endocrine therapyUp to 1 additional endocrine therapyMost recent endocrine treatment given for ≥6 months prior to disease progressionRadiological progression during or after the last line of therapyECOG performance status of 0 or 1Measurable disease evaluable per RECIST v1.1 or nonmeasurable bone-only disease	<ul style="list-style-type: none">Active brain metastasesAdvanced, symptomatic visceral spread at risk of life-threatening complications in the short termPrior treatment with:<ul style="list-style-type: none">VepdegestrantFulvestrantmTOR, PI3K, or AKT pathway inhibitorsPARP inhibitorsOther investigational novel endocrine therapyPrior CDK4/6 inhibitor treatment in the neoadjuvant/adjuvant settingChemotherapy for advanced/metastatic disease
AKT=protein kinase B; CDK=cyclin-dependent kinase; ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; mTOR=mammalian target of rapamycin; PARP=poly ADP ribose polymerase; PI3K=phosphoinositide-3 kinase; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1	

Table 2: VERITAC-2 outcome measures	
Primary objective	Endpoints
<ul style="list-style-type: none">Evaluate the clinical activity of vepdegestrant compared with fulvestrant	<ul style="list-style-type: none">PFS by blinded independent central review in:<ul style="list-style-type: none">ITT population<i>ESR1</i> mutation population
Secondary objectives	Endpoints
<ul style="list-style-type: none">Further evaluate the clinical activity of vepdegestrant compared with fulvestrant	<ul style="list-style-type: none">OSORR,^a DOR, and CBR^b
<ul style="list-style-type: none">Evaluate the safety and tolerability of vepdegestrant compared with fulvestrantEvaluate the effect of vepdegestrant on QTc	<ul style="list-style-type: none">Incidence of AEs, SAEs, and ECG and laboratory abnormalitiesQT interval
<ul style="list-style-type: none">Evaluate the PK of vepdegestrant	<ul style="list-style-type: none">Plasma concentration of vepdegestrant
<ul style="list-style-type: none">Evaluate the effects of vepdegestrant compared with fulvestrant on QoL	<ul style="list-style-type: none">EQ-5D-5LEORTC QLQ-C30EORTC QLQ-BR23BPI-SF
<ul style="list-style-type: none">Evaluate changes in tumor biomarkers with vepdegestrant compared with fulvestrant	<ul style="list-style-type: none">Circulating tumor DNA changes
^a Proportion of patients with confirmed complete response or partial response by blinded independent central review ^b Proportion of patients with confirmed complete response, partial response, or stable disease ≥24 weeks AE=adverse event; BPI-SF=Brief Pain Inventory-Short Form; CBR=clinical benefit rate; DOR=duration of response; ECG=electrocardiogram; EORTC QLQ-BR23=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Module; EORTC QLQ-C30=EORTC Quality of Life Questionnaire Core; EQ-5D-5L=EuroQol 5 Dimensions-5 Levels; ITT=intent-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics; QoL=quality of life; SAE=serious AE	