TPS1122

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

Background and Rationale

- Vepdegestrant (ARV-471) is an oral PROTAC ER degrader that binds to and degrades wild-type ER and clinically relevant mutants[1]
- Vepdegestrant directly binds the cereblon E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation, whereas SERDs indirectly recruit the ubiquitin-proteasome system, secondary to conformational changes and/or immobilization of ER[2]
- 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 fulvestrant[1]
- 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 cancer[6]
  - 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

[a]Rate of confirmed complete response, partial response, or stable disease ≥24 weeks; evaluable patients were enrolled ≥24 weeks prior to the data cutoff

Study Design

- In this open-label, global, multicenter, phase 3 study (**Figure 1**), patients are randomized 1:1 to receive vepdegestrant or fulvestrant in 28-day cycles
- 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**

Study Status

- Enrollment is ongoing
- Countries with currently open and planned study sites are shown in **Figure 2**

Please scan this QR code with your smartphone app to view a **plain language summary** of the poster

Please scan this QR code with your smartphone app to view a **video of the mechanisms of action of vepdegestrant and SERDs**

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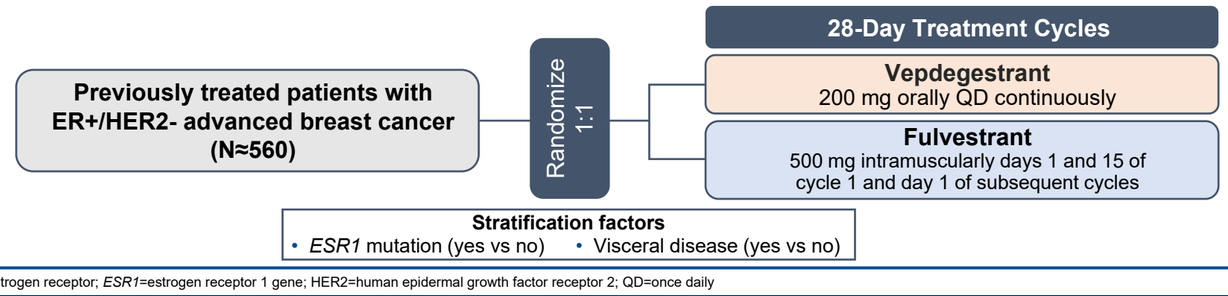
Figure 1: VERITAC-2 trial schema



ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; HER2=human epidermal growth factor receptor 2; QD=once daily

Table 1: VERITAC-2 key eligibility criteria

Inclusion criteria	Exclusion criteria
• Women or men aged ≥18 years • Confirmed ER+/HER2- locoregional recurrent or metastatic breast cancer • Prior therapies for locoregional recurrent or metastatic disease must fulfill all the following criteria: – 1 line of CDK4/6 inhibitor therapy in combination with endocrine therapy – Up to 1 additional endocrine therapy – Most recent endocrine treatment given for ≥6 months prior to disease progression – Radiological progression during or after the last line of therapy • ECOG performance status of 0 or 1 • Measurable disease evaluable per RECIST v1.1 or nonmeasurable bone-only disease	• Active brain metastases • Advanced, symptomatic visceral spread at risk of life-threatening complications in the short term • Prior treatment with: – Vepdegestrant – Fulvestrant – mTOR, PI3K, or AKT pathway inhibitors – PARP inhibitors – Other investigational novel endocrine therapy – Prior CDK4/6 inhibitor treatment in the neoadjuvant/adjuvant setting – Chemotherapy 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

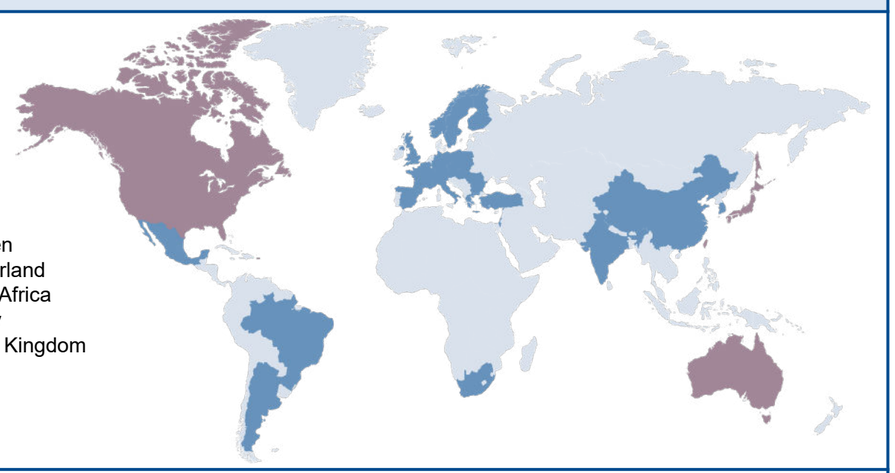
Primary objective	Endpoints
• Evaluate the clinical activity of vepdegestrant compared with fulvestrant	• PFS by blinded independent central review in: – ITT population – *ESR1* mutation population
Secondary objectives	**Endpoints**
• Further evaluate the clinical activity of vepdegestrant compared with fulvestrant	• OS • ORR,[a] DOR, and CBR[b]
• Evaluate the safety and tolerability of vepdegestrant compared with fulvestrant	• Incidence of AEs, SAEs, and ECG and laboratory abnormalities
• Evaluate the effect of vepdegestrant on QTc	• QT interval
• Evaluate the PK of vepdegestrant	• Plasma concentration of vepdegestrant
• Evaluate the effects of vepdegestrant compared with fulvestrant on QoL	• EQ-5D-5L • EORTC QLQ-C30 • EORTC QLQ-BR23 • BPI-SF
• Evaluate changes in tumor biomarkers with vepdegestrant compared with fulvestrant	• 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; *ESR1*=estrogen receptor 1 gene; ITT=intent-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics; QoL=quality of life; SAE=serious AE

Figure 2: VERITAC-2 study sites

Currently enrolling[a]:
- Australia (mainland and Tasmania)
- Canada
- Japan
- Puerto Rico
- Taiwan
- United States

Planned[b]:
- Argentina
- Austria
- Belgium
- Brazil
- Bulgaria
- China
- Czech Republic
- Finland
- France
- Germany
- Greece
- Hungary
- India
- Italy
- Israel
- Korea
- Norway
- Mexico
- Poland
- Slovakia
- Spain
- Sweden
- Switzerland
- South Africa
- Turkey
- United Kingdom



[a]Countries with study sites as of April 21, 2023
[b]As the study continues to enroll, additional sites will open, including within the EU and beyond

References

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