Clinical Study Report Synopsis	
Drug Substance	Capivasertib (AZD5363)
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A Phase III Double-blind Randomised Study Assessing the Efficacy and Safety of Capivasertib + Fulvestrant Versus Placebo + Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic Hormone Receptor Positive, Human Epidermal Growth Factor Receptor 2 Negative (HR+/HER2−) Breast Cancer Following Recurrence or Progression On or After Treatment with an Aromatase Inhibitor (CAPItello-291)

Study dates: First subject enrolled: 16 April 2020
Last subject last visit: 13 October 2021

Phase of development: Therapeutic confirmatory (III)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This Clinical Study Report (CSR) synopsis reports the primary progression-free survival (PFS) analysis, with a data cut-off (DCO) of 15 August 2022 (DCO1).

Study centres

Patients were randomised into 181 centres across 19 countries worldwide: Region 1 (112 centres), Region 2 (23 centres), Region 3 (46 centres).

Publications

Turner N, Howell S, Jhaveri K, Gomez H, Toi M, Hu X, et al. 350TiP: A phase III trial of capivasertib and fulvestrant versus placebo and fulvestrant in patients with HR+/HER2− breast cancer (CAPItello-291). Ann Oncol 2020;31(Suppl 4):S388-9.

Turner N, Oliveira M, Howell SJ, Dalenc F, Cortés J, Gomez H, et al. Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: results from the Phase III CAPItello-291 trial. Presented at: San Antonio Breast Cancer Symposium, 6-10 December 2022, San Antonio, Texas, USA (GS3-04).

Table S1 Objectives and Endpoints

Objectives [a]	Endpoints
Primary	
• To compare the effect of capivasertib + fulvestrant relative to placebo + fulvestrant by assessment of PFS in the overall population and in the *PIK3CA/AKT1/PTEN*-altered subgroup (see Protocol Version 4.0, Section 3).	• PFS is defined as the time from randomisation until progression per RECIST v1.1, as assessed by the investigator at the local site, or death due to any cause.
Secondary	
• To compare the effect of capivasertib + fulvestrant relative to placebo + fulvestrant by assessment of OS in the overall population and in the *PIK3CA/AKT1/PTEN*-altered subgroup (see Protocol Version 4.0, Section 3).	• OS is length of time from randomisation until the date of death due to any cause.
• To compare the effect of capivasertib + fulvestrant relative to placebo + fulvestrant by assessment of PFS2 in the overall population and in the *PIK3CA/AKT1/PTEN*-altered subgroup (see Protocol Version 4.0, Section 3).	• PFS2 is defined as the time from randomisation until second progression on next-line treatment, as assessed by the investigator at the local site, or death due to any cause.
• To compare the effect of capivasertib + fulvestrant relative to placebo + fulvestrant by assessment of ORR in the overall population and in the *PIK3CA/AKT1/PTEN*-altered subgroup (see Protocol Version 4.0, Section 3).	• ORR is defined as the percentage of patients with at least one CR or PR per RECIST v1.1, as assessed by the investigator at the local site.
• To compare the effect of capivasertib + fulvestrant relative to placebo + fulvestrant by	• DoR is defined as the time from the date of first documented response until date of documented

Objectives [a]	Endpoints
assessment of DoR in the overall population and in the *PIK3CA/AKT1/PTEN*-altered subgroup (see Protocol Version 4.0, Section 3).	progression or death in the absence of disease progression.
• To compare the effect of capivasertib + fulvestrant relative to placebo + fulvestrant by assessment of CBR in the overall population and in the *PIK3CA/AKT1/PTEN*-altered subgroup (see Protocol Version 4.0, Section 3).	• CBR is defined as the percentage of patients who have a CR, PR or stable disease per RECIST v1.1 (without subsequent cancer therapy) maintained ≥ 24 weeks after randomisation.
• To assess the safety and tolerability of capivasertib + fulvestrant as compared to placebo + fulvestrant in the overall population and in the *PIK3CA/AKT1/PTEN*-altered subgroup.	• Safety and tolerability will be evaluated in terms of AEs/SAEs, vital signs, clinical chemistry/haematology/ glucose metabolism parameters, and ECG parameters. For full details of the assessments, refer to Protocol Version 4.0, Table 3).
• To evaluate the PK of capivasertib when given in combination with fulvestrant.	• Plasma concentration of capivasertib pre-dose (C_{trough}) and post-dose (C_{1h} and C_{4h}) in the overall population (patients randomised to capivasertib + fulvestrant). • AUC_{0-12h}, C_{max} and t_{max} in a subpopulation of approximately 6 Japanese patients with rich PK sampling.
• To assess the impact of capivasertib + fulvestrant vs placebo + fulvestrant on patients' disease-related symptoms, function and HRQoL in the overall population and in the *PIK3CA/AKT1/PTEN*-altered subgroup where applicable (see Protocol Version 4.0, Section 3).	• Evaluation of EORTC QLQ-C30, EORTC QLQ-BR23, scale/item scores including change from baseline and time to deterioration.
• To compare the effect of capivasertib + fulvestrant relative to placebo + fulvestrant by assessment of time to definitive deterioration of ECOG performance status from baseline in the overall population and in the *PIK3CA/AKT1/PTEN*-altered subgroup (see Protocol Version 4.0, Section 3).	• Time to definitive deterioration of ECOG performance status is defined as time from randomisation to the earlier of the date of the first definitive deterioration or death due to any cause.

[a] [a] The *PIK3CA/AKT1/PTEN*-altered subgroup is referred to as the 'Altered Population' in this CSR.

CCI [redacted]

Study design

This was a Phase III, double-blind, placebo-controlled, parallel-group, randomised, multicentre study assessing the efficacy and safety of capivasertib + fulvestrant versus (vs) placebo + fulvestrant for the treatment of patients with locally advanced (inoperable) or metastatic hormone receptor-positive, human epidermal growth factor receptor 2 negative (HR+/HER2−) breast cancer following recurrence or progression on or after aromatase inhibitor (AI) therapy, with or without a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor.

Patients were randomly assigned to treatment in a 1:1 ratio using a randomisation scheme loaded into an interactive web response system (IWRS) system database, to receive treatment with capivasertib + fulvestrant or placebo + fulvestrant. Randomisation was stratified according to the following factors: liver metastases (yes vs no), prior use of CDK4/6 inhibitors (yes vs no), and geographic location (Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia).

Patients with a phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha/AKT1/phosphatase and tensin homolog (*PIK3CA/AKT1/PTEN*)-altered tumour (the Altered Population) were identified by post randomisation central testing of tumour tissue collected prior to randomisation based on a prespecified list of molecular alterations, using a validated assay.

At the start of the study, the primary objective was to compare the effect of capivasertib + fulvestrant relative to placebo + fulvestrant by assessment of PFS in the Overall Population and assessment of PFS in the Altered Population was a secondary objective, although the statistical multiple testing procedure made provision for type 1 error to be controlled at 5% for both the Overall Population and the Altered Population. Progression-free survival in the Altered Population was reclassified as a dual primary endpoint in a protocol amendment in line with the intent of the originally specified statistical testing strategy. The following secondary objectives were also changed during the course of the study to include assessment in the Altered Population as well as the Overall Population: overall survival (OS); time from randomisation to second progression or death (PFS2); objective response rate (ORR); duration of response (DoR); clinical benefit rate (CBR); patients' disease-related symptoms, function and health-related quality of life (HRQoL); and time to definitive deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG PS) from baseline.

This CSR (CSR Version 1) presents data from the primary PFS analysis of the Global cohort based on a DCO date of 15 August 2022 (DCO1), which occurred approximately 10 months after the last patient in this cohort was randomised.

Recruitment continued in China after the Global cohort last patient first visit (LPFV) (13 October 2021) until approximately 134 Chinese patients had been randomised into the China cohort. Patients recruited in China prior to the Global cohort LPFV were included in both the Global and China cohorts. The results from the China cohort are presented in a separate CSR.

Target population and sample size

Key inclusion criteria for the study were as follows:

- Adult females, pre- and/or post-menopausal, and adult males (aged ≥ 18 years [≥ 20 years in Japan]). Pre-menopausal (and peri-menopausal) women could be

enrolled if amenable to treatment with a luteinising-hormone releasing hormone (LHRH) agonist. Patients had to have commenced concomitant treatment with LHRH agonist prior to or on Cycle 1, Day 1 and be willing to continue it for the duration of the study.

- Histologically confirmed HR+/HER2− breast cancer determined from the most recent tumour sample (primary or metastatic), as per the American Society of Clinical Oncology and College of American Pathologists guideline recommendations. To fulfil the requirement of hormone receptor-positive (HR+) disease, a breast cancer had to express oestrogen receptor (ER) with or without co-expression of progesterone receptor.
- Metastatic or locally advanced disease with radiological or objective evidence of recurrence or progression (the cancer should have shown progression during or after most recent therapy); locally advanced disease must not have been amenable to resection with curative intent (patients who were considered suitable for surgical or ablative techniques following potential down-staging with study treatment were not eligible).
- Eastern Cooperative Oncology Group/World Health Organisation (ECOG/WHO) performance status 0 or 1 with no deterioration over the previous 2 weeks and life expectancy of ≥ 12 weeks.
- Patients were to have received treatment with an AI-containing regimen (single agent or in combination) and have:
  - Radiological evidence of breast cancer recurrence or progression while on, or within 12 months of the end of (neo)adjuvant treatment with an AI, OR
  - Radiological evidence of progression while on prior AI administered as a treatment line for locally advanced or metastatic breast cancer (this did not need to be the most recent therapy).
- Patients had to have measurable disease according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) and/or at least 1 lytic or mixed (lytic + sclerotic) bone lesion that could be assessed by computed tomography (CT) or magnetic resonance imaging (MRI); patients with sclerotic/osteoblastic bone lesions only in the absence of measurable disease were not eligible.
- Formalin-fixed paraffin-embedded (FFPE) tumour sample from primary or recurrent cancer for central testing.

Key exclusion criteria for the study were as follows:

- Prior treatment with fulvestrant or other selective oestrogen receptor degraders (SERDs), or AKT serine/threonine kinase (AKT), phosphatidylinositol-3-kinase (PI3K), or mammalian target of rapamycin (mTOR) inhibitors.
- Clinically significant abnormalities of glucose metabolism as defined by diabetes mellitus requiring insulin treatment, and/or glycosylated haemoglobin (HbA1C) ≥ 8.0% (63.9 mmol/mol).

- More than 2 lines of endocrine therapy for inoperable locally advanced or metastatic disease.
- More than 1 line of chemotherapy for inoperable locally advanced or metastatic disease.

Of note, to ensure the enrolled population was representative of the general AI-resistant HR+/HER2− advanced or metastatic breast cancer population, the study intended to enrol a minimum of 51% of patients previously treated with a CDK4/6 inhibitor.

The study was originally designed with a sample size that provides sufficient power to show a statistically significant difference between capivasertib + fulvestrant and placebo + fulvestrant in both PFS and OS in the Overall Population, as well as PFS in the Altered Population. Assuming a 12-month delay to a treatment effect and a hazard ratio (HR) of 0.64 after the delay, and a significance level of 5%, a total of 492 OS events were required to achieve 90% power to detect a treatment effect of an average HR 0.74 in the Overall Population. Assuming 70% maturity at the time of the OS final analysis, approximately 700 patients would need to be randomised. It was expected that, of these, a minimum of approximately 224 patients would test positive for tumours with *PIK3CA/AKT1/PTEN* alterations and be assigned to the Altered Population.

Assuming a significance level of 3.5%, a total of 542 PFS events (approximately 77% maturity) would provide > 99% power to detect a treatment effect of HR 0.64 in the Overall Population. Given the estimated sample size of the Altered Population and assuming a significance level of 5% following recycling of the remaining 3.5% alpha, a total of 217 PFS events (approximately 77% maturity) would provide 90.8% power to detect a treatment effect of HR 0.64 in the Altered Population. The China cohort was planned to consist of approximately 134 randomised patients. Recruitment continued in China until approximately 134 Chinese patients had been randomised. The results from the China cohort are presented in a separate CSR.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

- Capivasertib (AZD5363): 400 mg capivasertib (2 tablets of 200 mg) orally, twice daily (BD) (total daily dose 800 mg) on Days 1 to 4 in each week of a 28-day treatment cycle.
  - Capivasertib 160 mg tablets, batch numbers:
    AAAC, AAAD, AAAF-A, AAAG-A, AAAK, AAAH, AAAL
  - Capivasertib 200 mg tablets, batch numbers:
    BAAD, BAAE, BAAF, BAAG, BAAL-A, BAAN, BAAR
- Placebo**:** 2 tablets orally, BD on Days 1 to 4 in each week of a 28-day treatment cycle.

  - Placebo 160 mg tablets, batch numbers:
    CAAB, CAAC, CAAD
  - Placebo 200 mg tablets, batch numbers:
    DAAD, DAAF, DAAG, DAAL, DAAH, DAAM
- **Fulvestrant:** 500 mg fulvestrant via intramuscular injection on Day 1 of Weeks 1 and 3 of Cycle 1, and then on Day 1, Week 1 of each cycle thereafter. Commercial fulvestrant was obtained centrally.

Duration of treatment

Study treatment was continued until disease progression unless there was evidence of unacceptable toxicity, or if the patient requested to stop the study treatment.

Statistical methods

The statistical methods and planned analyses changed before DCO; these changes, including removal of the planned interim analysis of PFS, were documented in the protocol amendments and the Statistical Analysis Plan (SAP).

The null hypotheses for the primary time to event endpoint (PFS) are:

- there is no difference between capivasertib + fulvestrant and placebo + fulvestrant in the probability of a progression event in the Overall Population
- there is no difference between capivasertib + fulvestrant and placebo + fulvestrant in the probability of a progression event in the Altered Population.

The intention of the study was to demonstrate the superiority of capivasertib + fulvestrant over placebo + fulvestrant in either or both of the Overall and Altered Populations.

The dual primary endpoints were formally tested at DCO1. The dual primary endpoint PFS in the Overall Population based on the investigator RECIST v1.1 was analysed using a log-rank test stratified by geographic region, liver metastases, and prior use of CDK4/6 inhibitors for generation of the p-value and using a method that corresponds to the Breslow approach for handling ties. To estimate the effect of treatment, the HR together with its 95% confidence interval (CI) and CI adjusted for multiplicity were estimated from a stratified Cox proportional hazards model with the Efron method for handling ties and the stratification variables included in the strata statement and the CI calculated using the profile likelihood approach. A HR less than 1 favours capivasertib + fulvestrant. The dual primary endpoint, PFS in the Altered Population was analysed in the same way.

The key secondary endpoints of OS and ORR were not planned to be formally tested at DCO1. However, following a request by the Food and Drug Administration (FDA), a small alpha spend was applied to an assessment of no OS detriment at DCO1. The secondary

endpoints OS, PFS2 and time to definitive deterioration of Eastern Cooperative Oncology Group (ECOG) were analysed in the same way as the primary endpoints. The ORR was compared between capivasertib + fulvestrant vs placebo + fulvestrant using logistic regression models adjusting for the stratification factors; results were presented in terms of an odds ratio (an odds ratio greater than 1 will favour capivasertib + fulvestrant). Descriptive data were provided for the DoR and CBR.

For European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30), an outcome variable consisting of a score from 0 to 100 was derived for each of the symptom scales/scores, each of the functional domains, and the global measure of health status scale. Changes from baseline were analysed using a mixed model repeat measures analysis. The model included treatment, visit, treatment by visit interaction, and the stratification factors liver metastases, prior use of CDK4/6 inhibitors and geographic region as explanatory variables, and the baseline score and baseline score by visit as covariates; patient was included as a random effect. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire breast cancer specific module (EORTC QLQ-BR23) multi-item scores were transformed to a 0 to 100 scale; absolute and change from baseline values were summarised. Time to deterioration was analysed using a stratified log-rank test as described for PFS.

Safety data were presented using descriptive statistics, as appropriate, for the Safety Analysis Set (SAS) and the Altered Subgroup SAS. Deaths were reported for the Full Analysis Set (FAS).

Study population

The study recruited a population that reflected the target population. All patients in the Overall Population received prior endocrine-based therapy, and all had previously received an AI, as required. A total of 44.1% of patients had also previously received tamoxifen.

A total of 70.1% of patients had previously received CDK4/6 inhibitors.

As expected, most patients (62.6%) had received one prior line of therapy for advanced disease, thus receiving capivasertib/placebo + fulvestrant as second-line therapy. Prior chemotherapy for advanced breast cancer (ABC) was reported for 18.2% of patients.

The treatment arms were balanced for demographic and disease characteristics, except for minor differences in menopausal and diabetic status which are not expected to alter the conclusions of the study. The overall proportion of patients with *PIK3CA/AKT1/PTEN* alterations detected in their tumour samples (ie, the Altered Population) was 40.8%, which was consistent with expectations. *PIK3CA/AKT1/PTEN* alteration status was unknown in 15.0% of patients.

At the time of DCO1, a higher proportion of patients continued to receive treatment in the capivasertib + fulvestrant arm compared with the placebo + fulvestrant arm (20.0% vs 12.3%). The most common reason for discontinuing capivasertib/placebo was worsening of the patient's breast cancer.

Efficacy analysis populations

- Overall Population (FAS): All patients randomised into the study, excluding patients randomised in China after the global cohort LPFV.
  - Altered Population (Altered Subgroup FAS): Patients with a *PIK3CA/AKT1/PTEN*-altered tumour determined by central testing.
  - Non-altered Population (Non-altered Subgroup FAS): Patients in the Overall Population excluding patients with a *PIK3CA/AKT1/PTEN*-altered tumour determined by central testing.
    - CCI [redacted]
    - No Result Population (Unknown FAS) CCI [redacted] Patients in the Non-altered Population without a valid central test result.

Summary of efficacy results

- The study met both its dual primary endpoints. Treatment with capivasertib + fulvestrant resulted in clinically meaningful and statistically significant improvement in investigator-assessed PFS by RECIST v1.1 compared with placebo + fulvestrant in both the Overall Population and the Altered Population:
  - In the Overall Population, a 40% reduction in the risk of progression in favour of capivasertib + fulvestrant was observed (HR: 0.60; 95% CI: 0.51 – 0.71; $p < 0.001$). Median PFS was 7.2 months in the capivasertib + fulvestrant arm, compared with 3.6 months in the placebo + fulvestrant arm
  - In the Altered Population, a 50% reduction in the risk of progression in favour of capivasertib + fulvestrant was observed (HR: 0.50; 95% CI: 0.38 – 0.65; $p < 0.001$). Median PFS was 7.3 months in the capivasertib + fulvestrant arm, compared with 3.1 months in the placebo + fulvestrant arm.

- The results of the sensitivity analyses of PFS by Blinded Independent Central Review (BICR) in both the Overall Population (HR: 0.61; 95% CI: 0.50 – 0.73; $p < 0.001$) and the Altered Population (HR: 0.51; 95% CI: 0.38 – 0.68; $p < 0.001$) were consistent with those of the primary PFS analyses, demonstrating the robustness of the PFS improvement seen with capivasertib + fulvestrant.

- Investigator-assessed PFS improvement was also observed in the Non-altered Population CCI [redacted] and the No Result population); a 30% reduction in the risk of progression in favour of capivasertib + fulvestrant was

observed (HR: 0.70; 95% CI: 0.56 – 0.88). Median PFS was 7.2 months in the capivasertib + fulvestrant arm, compared with 3.7 months in the placebo + fulvestrant arm.

  - CCI
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- Results of secondary endpoints were supportive of the PFS results:
  - An assessment of no OS detriment at the time of the primary PFS analysis did not suggest a detrimental effect on survival of treatment with capivasertib + fulvestrant compared with placebo + fulvestrant in the Overall Population or the Altered Population.
  - Treatment with capivasertib + fulvestrant was associated with numerically higher ORR and CBR relative to placebo + fulvestrant arm in both the Overall Population and the Altered Population:
    - ORR: Overall Population 22.9% vs 12.2%; Altered Population 28.8% vs 9.7%
    - CBR: Overall Population 55.5% vs 32.4%; Altered Population 64.0% vs 29.4%
  - The results of PFS2 showed a numerical trend in favour of capivasertib + fulvestrant relative to the placebo + fulvestrant arm, in both the Overall Population and in the Altered Population:
    - In the Overall Population, a 30% reduction in the risk of second progression in favour of capivasertib + fulvestrant was observed (HR: 0.70; 95% CI: 0.57 – 0.86). The median PFS2 was prolonged by 2.2 months from 12.5 months in the placebo + fulvestrant group to 14.7 months in the capivasertib + fulvestrant group.
    - In the Altered Population, a 48% reduction in the risk of progression in favour of capivasertib + fulvestrant was observed (HR: 0.52; 95% CI: 0.38 – 0.71). The median PFS was prolonged by 4.7 months from 10.8 months in the placebo + fulvestrant group to 15.5 months in the capivasertib + fulvestrant group.

  - The median DoR was similar in both treatment arms (capivasertib + fulvestrant and placebo + fulvestrant): Overall Population median 9.8 months vs 8.4 months, respectively; Altered Population median 9.4 months vs 8.6 months, respectively.
  - Capivasertib + fulvestrant delayed the TFSC in both the Overall Population and the Altered Population:
    - In the Overall Population, the median TFSC was delayed by 4.2 months from 6.8 months in the placebo + fulvestrant arm to 11.0 months in the capivasertib + fulvestrant arm.
    - In the Altered population, the median TFSC was delayed by 5.0 months from 6.0 months in the placebo + fulvestrant arm to 11.0 months in the capivasertib + fulvestrant arm.
  - Although immature at the time of analysis, the results of the time to deterioration of ECOG PS were numerically in favour of capivasertib + fulvestrant compared with the placebo + fulvestrant arm, in both the Overall Population and the Altered Population.
- There was clinically meaningful worsening of diarrhoea across all cycles in the capivasertib + fulvestrant arm, as measured by the EORTC QLQ-C30. However, no clinically meaningful change was observed in global health status/QoL at any timepoint. Global health status/QoL (QoL) was also maintained for longer with capivasertib + fulvestrant than with placebo + fulvestrant. The treatment arms were comparable for the functional domains (role, physical, social, cognitive, and emotional functioning) and other symptom domains.

Summary of pharmacokinetic results

- Following a single oral dose, capivasertib was rapidly absorbed with a median time to reach peak or maximum observed concentration following drug administration (t_{max}) of 1.49 hours. The geometric mean maximum observed plasma (peak) concentration (C_{max}) was 1697 ng/mL, the geometric mean area under the plasma concentration-time curve from zero to 12 hours (AUC_{0-12h}) was 6050 h*ng/mL, and the variability was moderate (55% coefficient of variation [CV] and 45% CV, respectively) (n = 6).

Summary of safety results

- Median total (intended) treatment duration was longer in the capivasertib + fulvestrant arm (capivasertib 5.42 months, fulvestrant 5.75 months) than in the placebo + fulvestrant arm (placebo 3.58 months, fulvestrant 3.68 months).
- Overall, the nature and incidence of adverse events (AEs) reported in the capivasertib + fulvestrant arm were consistent with the known safety profiles of capivasertib and fulvestrant, or due to underlying disease.
  - The most common AEs reported in the capivasertib + fulvestrant arm (in ≥ 20% of patients) were diarrhoea, nausea, rash, fatigue and vomiting. The most commonly reported AEs of Common Terminology Criteria for Adverse Event (CTCAE) Grade 3

or above were diarrhoea, rash maculo-papular, rash, hyperglycaemia, and hypokalaemia. The incidence of AEs of maximum CTCAE Grade 4 was low (2.5%).

  - In the capivasertib + fulvestrant arm, the incidence of AEs with an outcome of death during the study period (including 30-day follow-up) was low (1.1%), and none were considered related to study treatment. The majority of reported deaths in the study were attributed to progression of disease and not to AEs.
  - The majority of capivasertib overdoses were single occurrences, occurred early on in treatment, and on non-dosing days. One patient had serious adverse events (SAEs) associated with an overdose (diabetic metabolic decompensation and renal failure).

- There was an overall slightly higher proportion of patients with renal AEs of potential interest in the capivasertib + fulvestrant arm; however, an assessment of Grade 3 AEs identified pre-existing risk factors for creatinine increase, including decreased hydration due to diarrhoea. The overall renal data did not provide evidence for a direct renal toxicity.

- Other AEs of potential interest related to hyperglycaemia were diabetic ketoacidosis (1 patient) and diabetic metabolic decompensation (2 patients). In each case, there were coexisting conditions or other confounders providing alternative explanations for the AEs.

- Overall, most AEs associated with capivasertib + fulvestrant could be managed with standard supportive treatments, dose interruptions, and/or dose reductions. Treatment discontinuation due to AEs was reported for 13% of patients.
  - The most commonly reported AEs (≥ 2% of patients) leading to capivasertib dose interruptions were diarrhoea, rash maculo-papular, rash, vomiting, hyperglycaemia, and nausea.
  - The most commonly reported AEs (≥ 2% of patients) leading to capivasertib dose reductions were diarrhoea and rash maculo-papular.
  - The most commonly reported AEs (≥ 1% of patients) leading to discontinuation of capivasertib were rash (grouped term), vomiting, diarrhoea, and pyrexia.
- Laboratory data showed the following:
  - There were more decreases in haemoglobin, lymphocytes and potassium, and increases in creatinine and glucose, in the capivasertib + fulvestrant arm compared with the placebo + fulvestrant arm, but the majority of laboratory results were Grades 1 and 2.
  - No notable increases in mean or median corrected QT interval (QTc) were observed. Three AEs of QTc prolongation (2 Grade 1, 1 Grade 3) were reported in the capivasertib + fulvestrant arm. No cases of sudden death or torsade de pointes were reported.

  - Overall, differences observed in laboratory values were not reflected in AE imbalances between treatment arms, either because they were not deemed clinically significant, or because they were linked to Adverse Events of Special Interest (eg, diarrhoea leading to hypokalaemia, hyponatraemia, hypernatraemia).
- There were no Hy's law cases during the study.
- Overall, addition of capivasertib to fulvestrant did not have a marked negative impact on treatment-related symptoms as assessed using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), except for diarrhoea. However, patient-reported overall tolerability, assessed by the Patient Global Impression–Treatment Tolerability (PGI-TT), suggests that most patients did not find the side effects of their cancer treatment very bothersome.

Conclusion(s)

- The study met both its dual primary endpoints. Treatment with capivasertib + fulvestrant resulted in clinically meaningful and statistically significant improvement in investigator-assessed PFS by RECIST v1.1 compared with placebo + fulvestrant in both the Overall Population and the Altered Population.
  - The results of the sensitivity analyses of PFS by BICR were consistent with those of the primary PFS analyses, demonstrating the robustness of the PFS improvement seen with capivasertib + fulvestrant.
  - Improvement in PFS in favour of treatment with capivasertib + fulvestrant compared with fulvestrant + placebo was consistently observed across all pre-specified subgroups, including prior exposure to CDK4/6 inhibitors.
  - CCI [redacted]
- Overall survival data were not mature at the time of the PFS primary analysis. There was no indication that treatment with capivasertib + fulvestrant had a detrimental effect on survival compared with placebo + fulvestrant in the Overall Population and the Altered Population.
- The results of the secondary efficacy variables PFS2, ORR, CBR, and ECOG PS were all in favour of capivasertib + fulvestrant relative to the placebo + fulvestrant arm, in both the Overall Population and the Altered Population, and thus supported the primary endpoints.
- Global health status/QoL was maintained for longer with capivasertib + fulvestrant than with placebo + fulvestrant, as measured by the EORTC QLQ-C30.
- Capivasertib in combination with fulvestrant has an acceptable safety and tolerability profile in patients with HR+/HER2- locally advanced or metastatic breast cancer following recurrence or progression on or after treatment containing an AI.

- The most commonly reported AEs were gastrointestinal disorders (diarrhoea, nausea, vomiting), rash, and fatigue. Most were CTCAE Grade 1 or 2 in severity, and were successfully managed with supportive treatments and/or capivasertib dose modification, suggesting good long-term tolerability. Few patients discontinued treatment due to these AEs.
- Most occurrences of hyperglycaemia AEs were during the first or second cycle of treatment, and were CTCAE Grade 1 or 2. Of those that required treatment, most were managed with antidiabetic medications. The laboratory data for HbA1C indicated good blood glucose control over time in the study population overall. Hyperglycaemic emergencies and severe complications (eg, diabetic ketoacidosis) were rare.
- The PGI-TT suggested that most patients did not find the side effects of their cancer treatment very bothersome.