Statistical Analysis Plan

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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)

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Abbreviation or special term	Explanation
AE	Adverse event
AI	Aromatase inhibitor
AESI	Adverse event of special interest
AKT1	Alpha serine/threonine-protein kinase 1
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Plasma concentration time curve (area under the curve)
BD	Twice daily
BICR	Blinded independent central review
BP	Blood pressure
BRCA 1/2	Breast cancer gene 1/2
CBR	Clinical benefit rate
CDK4/6	Cyclin-dependent kinases 4 and 6
CDx	Companion Diagnostic
CI	Confidence interval
CMH	Cochran-Mantel Haenszel
CR	Complete response
CRF	Case report form
CRO	Contract research organisation
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse event
ctDNA	Circulating tumour deoxyribonucleic acid
CV	Coefficient of variation
DAE	Discontinuation of investigational product due to adverse event
DBL	Database lock
DCO	Data cut-off
DoR	Duration of response
d.p.	Decimal place
ECG	Electrocardiogram

Abbreviation or special term	Explanation
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-BR23	EORTC Quality of Life Questionnaire-breast cancer specific module
EORTC QLQ-C30	EORTC Quality of Life Questionnaire-Core 30 items
EQ-5D	EuroQol 5-dimension
EQ-5D-5L	EuroQol 5-dimension, 5 level health state utility index
EQ-VAS	EuroQol visual analogue scale
ER	Estrogen receptor
FAS	Full analysis set
FFPE	Formalin-fixed paraffin-embedded
HER2	Human epidermal growth factor receptor 2
HL	Hy's Law
HOSPAD	Hospital resource use module
HR	Hazard Ratio
HR+	Hormone receptor positive
HRQoL	Health-related quality of life
IA	Interim analysis
ICF	Informed consent form
iCRO	Imaging contract research organisation
ICU	Intensive care unit
IDMC	Independent data monitoring committee
IHC	Immunohistochemistry
IMP	Investigational medicinal product
IPD	Important protocol deviation
IRC	Independent review charter
ITT	Intention to treat
IV	Intravenous
IVD	In-vitro diagnostic
IWRS	Interactive web response system
KM	Kaplan-Meier
LD	Longest diameter
LPFV	Last patient first visit
MedDRA	Medical dictionary for regulatory activities
min	Minute

Abbreviation or special term	Explanation
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
ms	Millisecond
mTOR	Mammalian target of rapamycin
MTP	Multiple testing procedure
NA	Not applicable
NE	Not evaluable
NED	No evidence of disease
NGS	Next generation sequencing
NL	New lesion
NTL	Non-target lesions
OAE	Other significant adverse events
ORR	Objective response rate
OS	Overall survival
PAP	Payer Analysis Plan
PD	Progressive disease
PFS	Progression free survival
PFS2	Time from randomisation to second progression or death
PGIC	Patient Global Impression - Change
PGIS	Patient Global Impression - Severity
PGI-TT	Patient Global Impression - Treatment Tolerability
PI3K	Phosphatidylinositol 3-kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PK	Pharmacokinetics
PR	Partial response
PRO	Patient reported outcome
PRO-CTCAE	Patient Reported Outcomes Common Terminology Criteria for Adverse Events
PS	Performance status
PT	Preferred term
PTEN	Phosphatase and tensin homolog
q4w	Every 4 weeks
QLQ-BR23	Quality of Life Questionnaire-breast cancer specific module
QLQ-C30	Quality of Life Questionnaire-Core 30 items
QoL	Quality of Life

Abbreviation or special term	Explanation
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Stable disease
SERD	Selective estrogen receptor degrader
SoA	Schedule of assessments
SOC	System organ class
TEAE	Treatment emergent adverse event
TFSC	Time to First Subsequent Chemotherapy
TL	Target lesion
TNM	Tumour, nodes, metastases classification
TSH	Thyroid stimulating hormone
TTD	Time to deterioration
ULN	Upper limit of normal
UTI	Urinary Tract Infection
VAS	Visual analogue scale
VHP	Voluntary Harmonisation Procedure
vs	Versus
WHO	World Health Organisation
WHO-DD	World Health Organisation drug dictionary

AMENDMENT HISTORY

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Multiple testing procedure and design characteristics	Nov 2022	Added an alpha spend of 0.0001 to both OS secondary endpoints at PFS DCO, updated section 4.2.1, section 5.1 and section 6	No	Updated per FDA request to allocate alpha for the assessment of OS KM curves
Primary or secondary endpoints	Aug 2022	Section 3.2.8 definition of TTD of ECOG updated	CSP v4	Details added/updated for programming to clarify the derivation
Statistical analysis method for the primary or secondary endpoints;	Aug 2022	Section 4.2.2 polling strategy updated	CSP v4	Added requirement of 2 responses/events in both treatment arm within any stratum to ensure the analysis is meaningful
Statistical analysis method for the primary or secondary endpoints;	Aug 2022	Section 4.2.4.8.1 P-value for MMRM analysis removed	CSP v4	P-value for MMRM analysis removed as the endpoint is not included in MTP for multiplicity control
Other	Aug 2022	Sections 3.2.2 and 3.5.14.3 Imputation rules for partial death dates updated	CSP v4	To align with CDx SAP v.3
Other	Aug 2022	Appendix B The look-up list table of qualifying mutations updated	CSP v4	Incorrect table included previously
Other: Violation and deviations	Aug 2022	Section 2.2 IPD list updated	CSP v4	To align with the most recent protocol deviation plan
Other	Aug 2022	Minor updates including updates for consistency between sections and typo corrections applied	Yes	Consistency and formatting
Primary endpoint; Multiple Testing Procedure; Data presentations;	Mar 2022	Section 4.2.1, 4.2.3, 4.2.7.1, 3.5.4 Removal of the interim PFS analysis for the overall population to align with the change to the dual	CSP v4	To align with CSP v4

		primary endpoints of PFS in the overall population and *PIK3CA/AKT1/PTEN*-altered sub-group; safety reports added for the altered sub-group		
Other: Safety data analysis	Mar 2022	Section 3.5.3, 4.2.7.5 New safety outputs added to support the dose; summaries for overdose added;	CSP v4	New safety analyses added on dose selection and overdose to further characterise dose; outputs added for the medical concept and for SMQ Torsades de pointes
Other: Violation and deviations	Mar 2022	Section 2.2 Section updated	CSP v4	To align with the most recent protocol deviation plan
Other: Document structure	Mar 2022	Section 4.2.4.8, 4.2.5.2 Secondary PRO endpoints EORTC QLQ-C30 and QLQ-BR23 moved from CCI [redacted] section 4.2.5.2; Subsections of 4.2.5.2 renumbered	CSP v3	To align the placement of the secondary PRO endpoints in the document structure with the study objectives.
Other: LPFV definition	Oct 2021	Section 1.3 LPFV definition clarified	Yes	Clarification on the global cohort recruitment completion.
Other: Analysis sets	Oct 2021	Section 2.1 FAS, Safety analysis set definition updated	CSP amendment	Clarified the FAS is to comprise patients randomised into the study, excluding patients randomised in China after the global cohort LPFV. More accurate wording used to describe actual study treatments. Definitions aligned with CSP wording.
Other: Analysis sets	Oct 2021	Section 2.1 China FAS and China SAS removed	CSP amendment	No analyses required for CSR on these populations.
Other: Analysis sets	Oct 2021	Section 2.1	Yes	Further clarity provided on biomarker test.

		Altered population definition updated;		
Other: Analysis sets	Oct 2021	Section 2.1 Japan PK set reserved for Japan PK outputs, Japan Intensive PK set added for PK rich PK population	Yes	Clarified to distinguish between all Japan patients set and a subset with rich PK sampling
Other: PD list updates	Oct 2021	Section 2.2 IPD list updated	Yes	Aligned with new IPD specification
Data presentations: Covid-19 items	Oct 2021	Section 2.2, Section 4.2.7.1, Section 4.2.10 COVID-19 related items, including disposition, demography, PD and safety summaries added	CSP amendment	To cover impact of COVID-19 pandemic
Derivation of primary or secondary endpoints	Oct 2021	Section 3.2.1 Two missed visits windows for PFS updated	Yes	Incorrect windows originally used
Derivation of primary or secondary endpoints	Oct 2021	Section 3.2.3 Censoring PFS2 events after 2 missed visits removed	Yes	Not applicable;
Derivation of primary or secondary endpoints	Oct 2021	Confirmed response definition added	Yes	Added to align with labelling requirements
Derivation of primary or secondary endpoints	Oct 2021	Section 3.2.6 CBR definition clarified	Yes	Alternative wording provided
Other: ECOG deterioration	Oct 2021	Section 3.2.8 Correction in ECOG deterioration definition	Yes	Deterioration is related with score increase rather than decrease.
Other: ECOG deterioration	Oct 2021	Section 3.2.8 Two missed visits windows details for ECOG deterioration added	Yes	Detailed derivations rules required for programming
Derivation of primary or secondary endpoints	Oct 2021	Section 3.3 Details on PRO analyses added	Yes	Use of on-treatment and follow-up assessments clarified

Derivation of primary or secondary endpoints	Oct 2021	Section 3.3.1 Details on missing items moved to proper section; derivations rules for subscale scores clarified; details on denominators added.	Yes	Incorrect placing; clarification for programming purposes.
Derivation of primary or secondary endpoints	Oct 2021	Section 3.3.1 PRO best overall response analyses removed	Yes	It is not a typical PRO endpoint. The value of this endpoint is questionable from the patients' perspective. These are lower priority analyses.
Derivation of primary or secondary endpoints	Oct 2021	Section 3.3.1 Time to HRQoL deterioration definition updated; Censoring rules for time to deterioration in PRO updated	Yes	Censoring for a start of subsequent therapy is removed to align with the MMRM analysis. Patients with no evaluable or missing baseline, or baseline outside the limits of 10 to 90 will be excluded
Other: PRO sensitivity	Oct 2021	Section 3.3.1 Sensitivity analysis for time to deterioration in PRO removed	Yes	Not required
Other: PRO improvement rate	Oct 2021	Section 3.3.1 Analyses of PRO improvement rates removed	Yes	Not required
Other: PRO EORTC QLQ-BR23	Oct 2021	Section 3.3.2 EORTC QLQ-BR23 score transformation derivation specified; meaningful change in functional scales added; details on denominators added.	Yes	Derivations specification was missing; Supportive analyses on mean change from baseline not required; clarification for programming purposes.
Other: PRO compliance	Oct 2021	Section 3.3.8 Definition of expected questionnaires updated; Over time summaries to be reported with at least 20 patients per arm	Yes	Updates made to account for the second progression during the PRO follow-up; Summaries over time will be presented only if there is sufficient number of

				observation collected. Aligned with the approach for safety endpoints.
Other: IMP exposure	Oct 2021	Section 3.5.1.1 Total exposure derivations updated; Actual exposure of Capivasertib or Placebo updated	Yes	Derivations were simplified; Planned no-dose periods removed from the derivation
Other: IMP exposure	Oct 2021	Section 3.5.1.2 Actual exposure of Fulvestrant updated	Yes	Actual exposure based on the intended exposure and duration of interruptions removed
Other: Safety data	Oct 2021	Section 3.5.13.2 Time windows for safety data updated	Yes	Clarification on post dose assessments on C1D1 and treatment discontinuation added; windowing corrected to align with the CSP, windowing for missing endpoints added
Other: Safety data	Oct 2021	Section 4.1 General notes on summary statistics over time updated	Yes	Summaries over time will be presented only if there is sufficient number of observation collected
Statistical analysis method for the primary or secondary endpoints;	Oct 2021	Section 4.2, Section 4.2.3.1, Section 4.2.4.1 Sensitivity analyses of primary and secondary endpoints adjusted for COVID-19 impact added	CSP amendment	To adjust the analysis for COVID-19 related deaths
Statistical analysis method for the primary or secondary endpoints;	Oct 2021	Section 4.2 Notes on statistical methods updated in Table 16	Yes	To align with the methods described in Analysis Methods section.
Statistical analysis method for the primary or secondary endpoints;	Oct 2021	Section 4.2.1 Multiplicity section aligned with CSP wording	Yes	One paragraph was missed.
Statistical analysis method for the primary or secondary endpoints;	Oct 2021	Section 4.2.2	Yes	CDK4/6 will be removed as the last one to reflect its importance.

		Order of dropping stratification factors in pooling strategy updated		
Statistical analysis method for the primary or secondary endpoints;	Oct 2021	Section 4.2.3.1, Section 4.2.4.1 CI adjusted for multiplicity added for primary and secondary endpoints presentations	Yes	To align with alpha spending approach
Other: PFS subgroup analyses	Oct 2021	Section 4.2.3.1 Subgroup variables list updated; Small subgroups may be combined	Yes	To include visceral metastases and smoking history, to specify source for liver metastases subgroups, to include more than 3 prior lines of therapies; categories with sparse data will be combined; race categories added
Other: PFS, consistency of treatment effects between subgroups	Oct 2021	Section 4.2.3.1. Interactions between treatment and stratification factors removed	Yes	Not required
Statistical analysis method for the primary or secondary endpoints	Oct 2021	Section 4.2.4.1 Kaplan-Meier plots for PFS in altered population added	Yes	In case IA results are positive, the plot may be needed to support ITT label.
Other: OS subgroup	Oct 2021	Section 4.2.4.2 By subgroup analysis within PIK3CA/AKT1/PTEN-altered population removed; Details on survival summaries added.	Yes	OS will be analysed by all subgroups as for PFS, including gene mutation status, but the subgroup analysis within the altered population is not required. This mistake is corrected with the current update. Overall survival estimates will be reported at different time points than for PFS due to longer observation time required.
Other	Oct 2021	Section 4.2.5.2 PRO analysis section renumbered	Yes	Formatting

Other: PRO missing data	Oct 2021	Section 4.2.5.2.1 The approach for data summaries in case of insufficient data added	Yes	20 observations threshold per arm at the visit will be used instead of excessive missing for simplicity; redundant wording removed
Other: PRO analyses	Oct 2021	Section 4.2.5.2.1 PRO MMRM analyses updated to include stratification factors	Yes	Analyses corrected to adjust for stratification factors
Other: PRO analyses	Oct 2021	Section 4.2.5.2.1 PRO analyses updated; BoR summaries and logistic regression model removed;	CSP amendment	Not required
Other: PRO analyses	Oct 2021	Section 4.2.5.2.2 Adjusted mean change from baseline analyses removed	Yes	Not required
Data presentation	Oct 2021	Section 4.2.5.3 and 4.2.5.4 PGIS, PGIC analyses made optional	Yes	CCI [redacted] and their main purpose is to serve as anchors for analyses to examine meaningful change on the EORTC QLQ-C30 and BR23. Not needed for CSR
Data presentations	Oct 2021	Section 4.2.7.1 Bullet list on death summaries updated	Yes	To align with the death summary template.
Data presentations	Oct 2021	Section 4.2.7.2 Clarification for multiple occasions of AESI within the same PT added	Yes	Clarification for programming purposes
Other: Safety variables	Oct 2021	Section 4.2.7.5 Liver tests evaluations appearance updated	Yes	To align with Hy's law definition
Other	Oct 2021	Appendix B added on *PIK3CA/AKT1/PTEN*-altered subgroup definition	Yes	Missed in the original version

Other	Oct 2021	Minor updates including Tables and Figures numbering, labelling and typo corrections applied	Yes	Formatting

* Pre-specified categories are
Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other

1 STUDY DETAILS

This statistical analysis plan (SAP) contains a more detailed description of the analyses in the clinical study protocol (CSP). This SAP is based on version 4.0 of the CSP.

1.1 Study objectives

Table 1 Study objectives

Primary objective	**Endpoint**
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.	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.

PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; vs, versus.

Secondary objective:	**Endpoint/Variable:**
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.	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.	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.	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 assessment of DoR in the overall population and in the *PIK3CA/AKT1/PTEN*-altered subgroup.	DoR is defined as the time from the date of first documented response until date of documented 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.	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/AKT/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. Assessments related to AEs cover:

	• Occurrence/frequency • Relationship to capivasertib and fulvestrant as assessed by investigator • CTCAE grade • Seriousness • Death • AEs leading to discontinuation of capivasertib/placebo • AEs leading to discontinuation of fulvestrant • AEs leading to dose interruption of capivasertib/placebo • AEs leading to dose interruption of fulvestrant • AEs leading to dose reduction of capivasertib/placebo • AEs of special interest • Other significant AEs Vital signs parameters include systolic and diastolic blood pressure, pulse, respiratory rate, body temperature and weight. Assessments cover: • Observed value • Absolute and change from baseline values over time
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 $_{0\text{-}12h}$, 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.	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	Time to definitive deterioration of ECOG performance status is defined as time from

overall population and in the *PIK3CA/AKT1/PTEN*-altered subgroup.	randomisation to the earlier of the date of the first definitive deterioration or death due to any cause.

AE, adverse event; C, concentration; CBR, clinical benefit rate; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Event; ctDNA, circulating tumour DNA; DoR, duration of response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; EORTC QLQ-BR23, EORTC Quality of Life Questionnaire breast cancer specific module; EORTC QLQ-C30, EORTC Quality of Life Questionnaire-Core 30 items; HRQoL health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, time from randomisation to second progression or death; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene; PK, pharmacokinetics; PR, partial response; PTEN, phosphatase and tensin homolog; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SAE, serious adverse event; vs, versus.

[a] CCI

BRCA1/2, breast cancer gene 1/2; ctDNA, circulating tumour DNA; DNA, deoxyribonucleic acid; EQ-5D-5L, European Quality of Life 5-Domain 5-Level Scale; IHC, immunohistochemistry; IVD, in vitro diagnostic; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival; PGIC, Patient Global Impression–Change; PGIS, Patient Global Impression–Severity; PGI-TT, Patient Global Impression–Treatment Tolerability; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; RNA, ribonucleic acid; TFSC, time to first subsequent chemotherapy or death; vs, versus.

1.2 Study design

This is a Phase III, double-blind, randomised study assessing the efficacy of capivasertib + fulvestrant vs placebo + fulvestrant for the treatment of patients with locally advanced (inoperable) or metastatic HR+/HER2− breast cancer following recurrence or progression on or after AI therapy. The study is powered to show a statistically significant difference between

capivasertib + fulvestrant and placebo + fulvestrant in PFS in the overall population and the *PIK3CA/AKT1/PTEN*-altered populations (dual primary endpoint)) and OS (key secondary endpoint) in the overall population and in the *PIK3CA/AKT/PTEN*-altered sub-population will be assessed.

The list of eligible variants will be defined and specified in Appendix B, prior to the PFS primary analysis.

Recruitment of patients to China cohort (at NMPA-certified sites in mainland China and outside China) will continue until approximately 134 patients have been randomised, irrespective of whether or not the overall study enrolment has been reached. This is to ensure adequate participation of Chinese patients to satisfy China Regulatory Authority requirements.

Patients will receive weekly capivasertib (400 mg or placebo, oral, twice daily; 4 days on and 3 days off) and fulvestrant (at the approved dose regimen [500 mg intramuscular injections on Day 1 of Weeks 1 and 3 of Cycle 1, and then on Day 1, Week 1 of each cycle thereafter]).

All patients will attend a screening visit a maximum of 28 days prior to the start of study treatment.

Day 1 is defined as the randomisation date; study treatment should begin as soon as possible after randomisation, ideally the same day. Randomised patients will continue study treatment until objective radiological disease progression as defined by Response Evaluation Criteria in Solid Tumours version 1 (RECIST v1.1), unacceptable toxicity occurs, the patient withdraws consent or death. Following objective disease progression, further treatment options will be at the discretion of the investigator. If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression, the patient should continue to be followed until objective disease progression as defined by RECIST v1.1. Cross-over from placebo to capivasertib is not allowed.

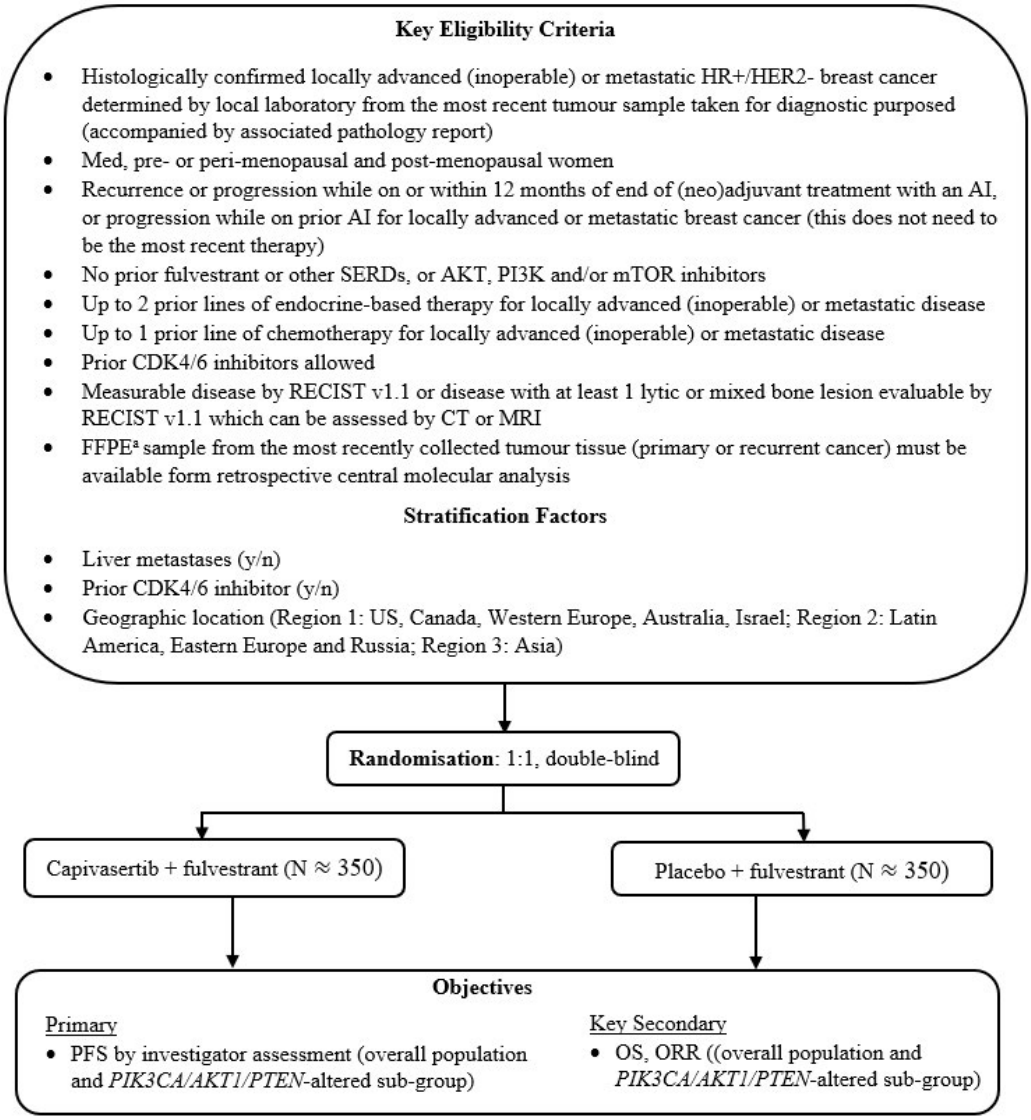
The randomisation scheme will be stratified on the following factors:

- Liver metastases (yes vs no)
- Prior use of CDK4/6 inhibitors (yes vs no)
  - Patients may have received prior treatment with CDK4/6 inhibitors as part of standard treatment or within clinical trials (in the latter scenario, written confirmation of exposure to the investigational agent rather than placebo is required to allow stratification at randomisation)
- Geographic location:
  - Region 1: United States, Canada, Western Europe, Australia, and Israel
  - Region 2: Latin America, Eastern Europe and Russia
  - Region 3: Asia

The dual primary endpoint, PFS, is defined as the time from randomisation until disease progression based on the investigator's assessment according to RECIST v1.1, or death due to any cause regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression in the overall and *PIK3CA/AKT1/PTEN*-altered populations. The key secondary endpoint of OS is defined as the time from the date of randomisation until death due to any cause in both the overall and *PIK3CA/AKT1/PTEN* altered subgroup. A sensitivity analysis will be conducted in the overall population and the *PIK3CA/AKT1/PTEN*-altered populations using PFS assessed by blinded, independent central review (BICR) and defined using RECIST v1.1 criteria.

The study design is summarised in Figure 1 and a study flow chart is illustrated in Figure 2.

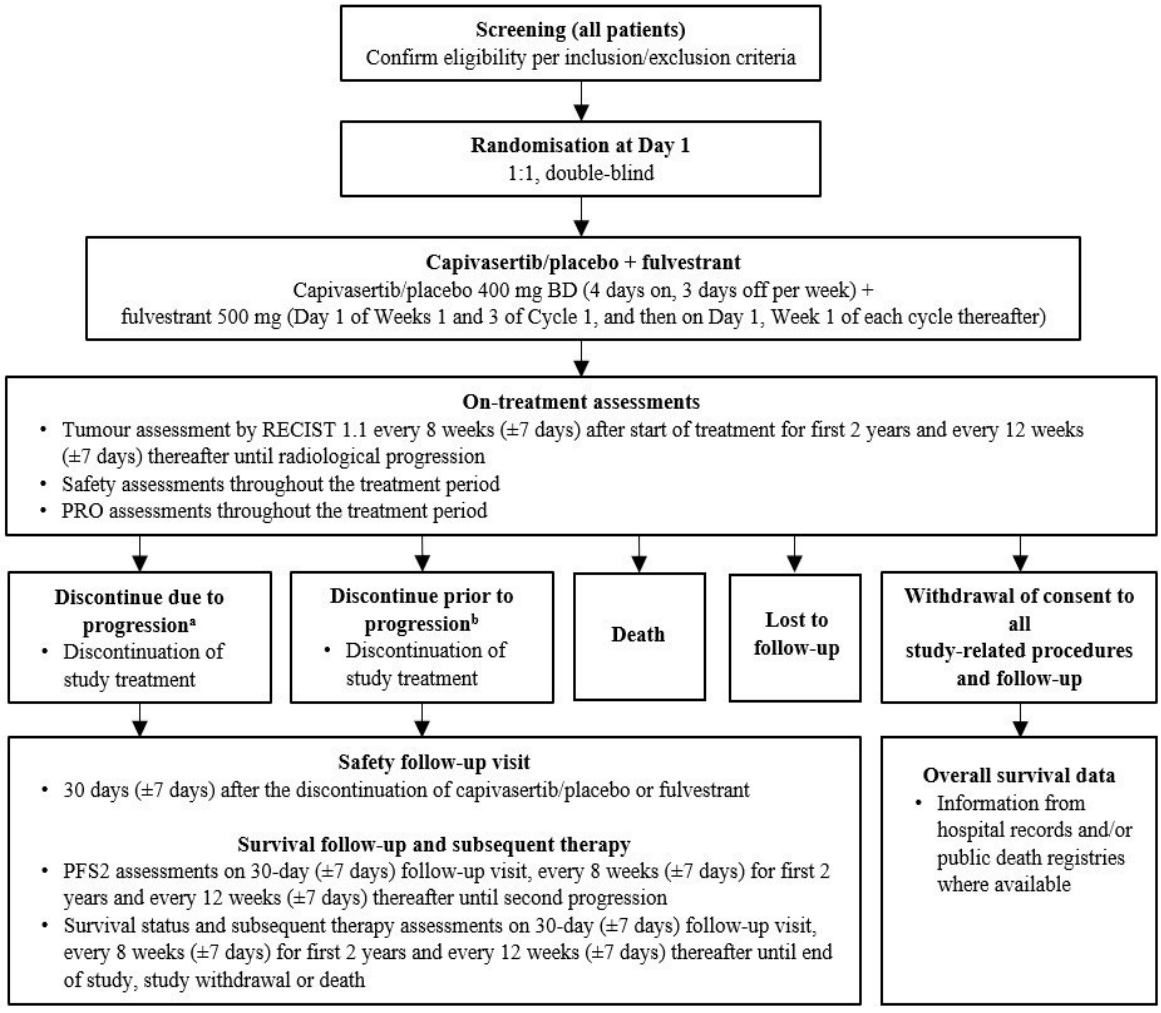
Figure 1 Study design



[a] FFPE (formalin-fixed, paraffin-embedded) blocks are strongly preferred, or if not possible, preferably 30 [minimal 20]) freshly-cut unstained serial tumour tissue sections are acceptable provided that they meet the specifications described in the Diagnostic Testing Manual.

AI, aromatase inhibitor; AKT, serine/threonine specific protein kinase; CBR, clinical benefit rate; CDK, cyclin dependent kinase; CT, computerised tomography; FFPE, formalin-fixed paraffin-embedded; HER2, human epidermal growth factor receptor 2; HR, Hormone receptor; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin, ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphatidylinositol-3-kinase; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SERD, selective estrogen response degrader; US, United States.

Figure 2 Study flow chart



BD, twice daily; PFS2, progression-free survival; PRO, patient-reported outcome; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

[a] If the patient discontinues due to progression, PROs (not including PGI-ITT and PRO-CTCAE) should be assessed at progression and every 4 weeks (±3 days) post discontinuation until PFS2.

[b] Patients who discontinue treatment prior to progression should continue to be scanned by RECIST v1.1 every 8 weeks (±7days) for the first two years and every 12 weeks (±7 days) thereafter until progression, regardless of reason for treatment discontinuation. If the patient discontinues due to toxicity but does not progress, PROs (not including PGI-ITT and PRO-CTCAE) should be assessed every 4 weeks (±3 days) until progression, at progression and every 4 weeks (±3 days) post progression until PFS2.

Further analyses for validation of the companion diagnostic (CDx) for non-China patients whose tumours harbour an eligible *PIK3CA/AKT1/PTEN* alteration will be detailed in a separate CDx SAP.

1.3 Number of subjects

It is expected that an estimated 930 patients will be screened so that approximately 700 patients can be randomised 1:1, with approximately 350 included in each arm. Of these 700 randomised patients, based on a prevalence of 40% to 45% for *PIK3CA/AKT1/PTEN* alterations (Cristofanilli et al 2016, Curtis et al 2012, Di Leo et al 2018, Hortobagyi et al 2016, Pereira et al 2016, Spoerke et al 2016), and a test failure rate of 20%, it is expected that a minimum of 224 patients will test positive for tumours with these alterations and will be assigned to the *PIK3CA/AKT1/PTEN*-altered subgroup. The prevalence of *PI3KCA/AKT1/PTEN* mutation status will be monitored post-randomisation by central testing of formalin-fixed paraffin-embedded (FFPE) tumour samples collected before study entry. Given the proposed sample size (approximately 700 patients overall), it is expected that randomisation will be sufficient to ensure a balance between treatment arms with respect to mutational status. Enrolment will be open to all eligible patients irrespective of the *PIK3CA/AKT1/PTEN* status of their tumour(s); however adequate tumour tissue collected before study entry will be required for a central retrospective analysis.

Recruitment of patients to China cohort (at NMPA-certified sites in mainland China and outside China) will continue until approximately 134 patients have been randomised, irrespective of whether or not the overall study enrolment has been reached. This is to ensure adequate participation of Chinese patients to satisfy China Regulatory Authority requirements.

Global recruitment will be completed once approximately 700 patients have been randomised. The LPFV is defined as the randomisation visit (date of IxRS transaction) of the last patient randomised into the global cohort. Global cohort will consist of patients recruited by the documented date of LPFV, except screen failed patients from China enrolled by the date of LPFV. Patients randomised in the NMPA-certified sites without a valid biomarker test result will be excluded from the global altered subgroup. Patients from other countries will be included in the global cohort regardless of the validity of the biomarker test result. The recruitment across all sites will then be closed except for those sites from China cohort, where recruitment of patients may continue.

If the global cohort completes the recruitment of approximately 700 randomised patients prior to the recruitment completion for Chinese cohort of approximately 134 randomised patients, then recruitment of the Chinese cohort will continue, and the global recruitment will be stopped. Recruitment on the Taiwanese NMPA certified sites (in addition to mainland China) may continue and these Taiwanese patients, recruited post the global cohort completion, will only contribute to the China cohort.

2 ANALYSIS SETS

"Randomised" patients are defined as those who undergo randomisation and receive a randomisation number. "Enrolled" patients are defined as those who sign informed consent. Analysis sets for China cohort will be used for endpoints in China analysis only, and detailed analysis plan will be provided in the China SAP.

2.1 Definition of analysis sets

Full Analysis Set (FAS)

This comprises all patients randomised into the study, excluding patients randomised in China after the global cohort last patient first visit (LPFV).

The FAS will be analysed according to randomised treatment regardless of the treatment received (intention-to-treat [ITT] principle). Patients who are randomized but did not subsequently receive treatment are included in the FAS. The FAS will be used as the primary population for reporting efficacy data (including patient reported outcomes [PROs]) and to summarise baseline characteristics.

Safety Analysis Set

The safety analysis set comprises all patients included in the FAS who received at least 1 dose of study drug (fulvestrant, capivasertib, placebo) and will be analysed according to the treatment received. If a patient receives at least 1 dose of capivasertib, they will be summarised in the capivasertib arm for safety summaries (e.g. capivasertib arm will include patients randomised to capivasertib who receive at least 1 dose of capivasertib, or placebo patients who receive at least 1 dose of capivasertib in error at any time). If a patient randomised to capivasertib receives only placebo treatment, then they will be summarised as part of the placebo arm. Patients who receive only fulvestrant will also be included in the safety analysis set and will be included in the treatment arm to which they were randomised.

Altered Subgroup FAS

All patients included in the FAS with a *PIK3CA/AKT1/PTEN*-altered tumour determined by central testing.

Altered Subgroup Safety Analysis Set

All patients included in the Safety Analysis Set with a *PIK3CA/AKT1/PTEN*-altered tumour determined by central testing.

Pharmacokinetic (PK) Analysis Set

All patients randomised in the global cohort who received at least 1 dose of capivasertib with at least one reportable concentration.

Japan Intensive Pharmacokinetic (PK) Analysis Set

All Japanese patients with rich PK samples, who received at least 1 dose of capivasertib and with at least one reportable concentration.

Table 2 Summary of outcome variables and analysis sets

Outcome variable	*Analysis set*
Efficacy Data	
PFS	*FAS and Altered Subgroup FAS*
OS	*FAS and Altered Subgroup FAS*
PFS2	*FAS and Altered Subgroup FAS*
ORR*, DoR*, CBR, Time to definitive deterioration of ECOG status, TFSC	*FAS and Altered Subgroup FAS*
Disease-related symptoms EORTC-QLQ, HRQoL	*FAS and Altered Subgroup FAS*
Healthcare Resource Use Module, PRO-CTCAE, PGI-TT, PGIS, PGIC	*FAS and Altered Subgroup FAS for PGIS and PGIC* *Safety and Altered Safety Analysis Set for PRO-CTCAE and PGI-TT*
Study Population/Demography Data	
Demography characteristics (e.g. age, sex etc.)	*FAS* and *Altered Subgroup FAS*
Baseline and disease characteristics	*FAS* and *Altered Subgroup FAS*
Important deviations	*FAS and Altered Subgroup FAS*
Medical/surgical history	*FAS* and *Altered Subgroup FAS*
Previous anti-cancer therapy	*FAS* and *Altered Subgroup FAS*
Concomitant medications/procedures	*FAS* and *Altered Subgroup FAS*
Subsequent anti-cancer therapy	*FAS* and *Altered Subgroup FAS*
PK Data	
PK data	*PK and Japan Intensive Pharmacokinetic Analysis Set*

Outcome variable	*Analysis set*
Safety Data	
Exposure	*Safety and Altered Safety Analysis Set*
Adverse events	*Safety and Altered Safety Analysis Set*
Laboratory measurements	*Safety and Altered Safety Analysis Set*
Vital signs	*Safety and Altered Safety Analysis Set*
ECGs	*Safety and Altered Safety Analysis Set*
ECHO/LVEF	*Safety and Altered Safety Analysis Set*

[*] Patients who are evaluable for the analysis of ORR are those with measurable disease at baseline. Patients who are evaluable for the analysis of DoR are those who responded in the ORR analysis.

2.2 Violations and deviations

For this study, the following general categories will be considered important protocol deviations (IPDs). These will be listed and summarised by randomised treatment group and discussed in the clinical study report (CSR) as appropriate:

- Subject randomised but who did not receive study treatment (Deviation 1).
- Patients who deviate from key entry criteria per the Clinical Study Protocol (Inclusion criteria 2, 6, 7, 8, 9, 11 & 13; Exclusion criteria 2, 5,10, 14, 20, 21 & 22) (Deviation 2).

  - Inclusion 2 - Provision of signed and dated, written ICF prior to any mandatory study specific procedures, sampling, and analyses

  - Inclusion 6 - 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 (Hammond et al 2010, Wolff et al 2018). To fulfil the requirement of HR+ disease, a breast cancer must express ER with or without co-expression of progesterone receptor. Therefore, tumours must be:

    - ER+ defined as ≥ 1% of tumour cells stain positive for ER on immunohistochemistry (IHC) or, if no percentage is available, then an Allred IHC score of ≥ 3/8,

    - Progesterone receptor positive defined as ≥1% of tumour cells stain positive for progesterone receptor on IHC or, if no percentage is available, then an Allred IHC score of ≥ 3/8; or progesterone receptor negative defined as < 1%

of tumour cells stain positive for progesterone receptor on IHC or, if no percentage is available, then an Allred IHC score of ≤2/8; or progesterone receptor unknown, and

- HER2− defined as 0 or 1+ intensity on IHC, or 2+ intensity on IHC and no evidence of amplification on in situ hybridisation (ISH)

- Inclusion 7 - Metastatic or locally advanced disease with radiological or objective evidence of recurrence or progression; locally advanced disease must not be amenable to resection with curative intent (patients who are considered suitable for surgical or ablative techniques following potential down-staging with study treatment are not eligible)

- Inclusion 8 - Patients are to have received treatment with an AI containing regimen (single agent or in combination) and have:

  (a) 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
  (b) Radiological evidence of progression while on prior AI administered as a treatment line for locally advanced or metastatic breast cancer (this does not need to be the most recent therapy)

- Inclusion 9 - Patients must have:

  - at least 1 lesion, not previously irradiated, that can be measured accurately at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with CT or MRI which is suitable for accurate repeated measurements, OR

  - in absence of measurable disease as defined above, at least 1 lytic or mixed (lytic + sclerotic) bone lesion that can be assessed by CT or MRI; patients with sclerotic/osteoblastic bone lesions only in the absence of measurable disease are not eligible

- Inclusion 11 - Consent to submit and provide a mandatory FFPE tumour sample for central testing. A FFPE tissue block from the most recently collected pre-randomisation tumour sample (primary or recurrent cancer) is preferred. If it is not possible to provide a tissue block, 30 (minimum 20) freshly-cut unstained serial tumour slides are to be provided. Local pathology QC must be completed prior to

randomisation to ensure the sample is suitable for next-generation sequencing (NGS) analysis, based on the requirements described in the Diagnostic Testing Manual

- Inclusion 13 - Eastern Cooperative Oncology Group (ECOG)/ World Health Organisation (WHO) performance status 0 or 1 with no deterioration over the previous 2 weeks and life expectancy of ≥ 12 weeks

- Exclusion 2 - Malignancies other than breast cancer within 5 years prior to study treatment initiation (except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma or Stage I endometrioid uterine cancer)

- Exclusion 5 - With the exception of alopecia, any unresolved toxicities from prior therapy greater than CTCAE grade 1 at the time of starting study treatment

- Exclusion 10 - Clinically significant abnormalities of glucose metabolism as defined by any of the following:

    - Patients with diabetes mellitus type 1 or diabetes mellitus type 2 requiring insulin treatment

    - HbA1c ≥ 8.0% (63.9 mmol/mol)

- Exclusion 14 - Refractory nausea and vomiting, malabsorption syndrome, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection, or other condition that would preclude adequate absorption of capivasertib

- Exclusion 20 - More than 2 lines of endocrine therapy for inoperable locally advanced or metastatic disease

- Exclusion 21 - More than 1 line of chemotherapy for inoperable locally advanced or metastatic disease. Adjuvant and neoadjuvant chemotherapy are not classed as lines of chemotherapy for ABC

- Exclusion 22 - Prior treatment with any of the following:

    - AKT, PI3K and mTOR inhibitors

    - Fulvestrant, and other SERDs

- Nitrosourea or mitomycin C within 6 weeks prior to study treatment initiation
- Any other chemotherapy, immunotherapy, immunosuppressant medication (other than corticosteroids) or anticancer agents within 3 weeks prior to study treatment initiation. A longer washout period may be required for drugs with a long half-life (e.g., biologics) as agreed by the sponsor
- Potent inhibitors or inducers of CYP3A4 within 2 weeks prior to the first dose of study treatment (3 weeks for St John's wort) or drugs that are sensitive to CYP3A4 inhibition within 1 week prior to study treatment initiation. For details, see Appendix D of CSP.
- Any concomitant medication that may interfere with fulvestrant safety and efficacy based on the prescribing information of fulvestrant and local clinical guidelines

- Non-compliance with screening procedure protocol requirements (RECIST 1.1 tumour assessment not performed or not performed within screening period of 28 days). (Deviation 3).
- No baseline RECIST v1.1 assessment on or before date of randomisation (Deviation 4).
- Non-compliance with protocol restrictions (e.g. use of prohibited medication or prohibited anti-cancer treatment therapy or wash out periods not respected (including St Johns Wort) (Deviation 5). Please refer to the CSP Section 6.5.2 and 6.5.3 for those medications that are detailed as being 'excluded' from permitted use during the study. This will be used as a guiding principle for the physician review of all medications prior to database lock.
- Fulvestrant administered 4 or more days prior planned per protocol/label date (D28 or D14 depending on cycle).
- Randomised patients received fulvestrant total daily dose not equal to 500 mg during any cycle.
- Randomised patients received capivasertib/placebo at incorrect dose for more than 4 days during any treatment cycle.
- Randomised patients received capivasertib/placebo at an alternative study treatment to that which they were randomized (only if changed to different arm).

Patients who receive the wrong treatment at any time will be included in the safety analysis set as described in Section 2.1. During the study, decisions on how to handle errors in treatment dispensing (with regard to continuation/discontinuation of study treatment or, if

applicable, analytically) will be made on an individual basis with written instruction from the study team leader and/or statistician.

The important protocol deviations will be listed and summarised by randomised treatment group. Deviation 1 (patients randomised but who did not receive capivasertib or matching placebo) will lead to exclusion from the safety analysis set. None of the other deviations will lead to patients being excluded from the analysis sets described in Section 2.1 (with the exception of the PK analysis set, if the deviation is considered to impact upon PK).

A per-protocol analysis excluding patients with specific important protocol deviations is not planned; however, a 'deviation bias' sensitivity analysis may be performed on the PFS endpoint excluding patients with deviations that may affect the efficacy of the trial therapy if > 10% of patients in either treatment group:

- Did not have the intended disease or indication or
- Did not receive any randomised therapy.

Protocol deviations related to COVID-19 infection will be listed and summarized, including missed visits and study drug interruptions or delays.

The need for such a sensitivity analysis will be determined following review of the protocol deviations ahead of database lock and will be documented prior to the primary analysis being conducted.

In addition to the programmatic determination of the deviations above, other study deviations captured from the case report form (CRF) module for inclusion/exclusion criteria will be tabulated and listed. Any other deviations from monitoring notes or reports will be reported in an appendix to the CSR.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Derivation of RECIST Visit Responses

For all patients, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST version 1.1 (Appendix A of CSP). It will also be used to determine if, and when a patient has progressed in accordance with RECIST v1.1.

Baseline radiological tumour assessments are to be performed no more than 28 days before the date of randomisation and ideally as close as possible to the start of study treatment. Afterward, CT or MRI scans of the chest, abdomen and pelvis (with additional anatomy as clinically indicated by extent of disease) will be repeated every 8 weeks (±7 days) for the first 18 months and every 12 weeks (±7 days) thereafter, after start of treatment (Cycle 1, Week 1,

Day 1) until objective radiological disease progression as defined by RECIST v1.1 (regardless of reason for treatment discontinuation).

If an unscheduled assessment is performed (e.g., to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to perform the subsequent image acquisition at the next scheduled imaging visit.

Patients who discontinue treatment prior to RECIST v1.1 progression (e.g., discontinuation due to toxicity or clinical progression) should continue to be scanned until confirmed RECIST v1.1 progression. The same imaging modality and the same assessment (e.g., the same contrast protocol for CT scans) should be performed at baseline and at all follow-up time-points.

From the investigator's review of the imaging scans, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST version 1.1. At each visit, patients will be programmatically assigned a RECIST v1.1 visit response of CR, PR, SD or PD, using the information from target lesions (TLs), non-target lesions (NTLs) and new lesions and depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment that cannot be evaluated then the patient will be assigned a visit response of not evaluable (NE), (unless there is evidence of progression in which case the response will be assigned as PD).

Please refer to Section 3.1.3 for the definitions of overall visit responses - CR, PR, SD and PD.

RECIST v1.1 outcomes (i.e. PFS, ORR etc.) will be calculated programmatically for the site investigator data (as described for endpoints in Section 3.2) from the overall visit responses.

3.1.1 Target lesions (TLs) - site investigator data

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD), (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. A patient can have a maximum of five measurable lesions recorded at baseline with a maximum of two lesions per organ (representative of all lesions involved and suitable for accurate repeated measurement) and these are referred to as target lesions (TLs). If more than one baseline scan is recorded, then measurements from the one that is closest and prior to first dose/administration of study medication will be used to define the baseline sum of TLs. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible

measurement. In which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

All other lesions (or sites of disease) not recorded as TL should be identified as non-target lesions (NTLs) at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits.

TL visit responses are described in Table 3 below.

Table 3 TL Visit Responses (RECIST v1.1)

Visit Responses	Description
Complete response (CR)	Disappearance of all TLs. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of TLs and an absolute increase of ≥ 5 mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not evaluable (NE)	Only relevant in certain situations (i.e. if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit; and scaling up could not be performed for lesions with interventions). Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.
Not applicable (NA)	No TLs are recorded at baseline.

Rounding of TL data

For calculation of PD and PR for TLs percentage changes from baseline and previous minimum should be rounded to one d.p. before assigning a TL response. For example, 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Lymph nodes

For lymph nodes, if the size reduces to < 10 mm then these are considered non-pathological. However, a size will still be given, and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are < 10 mm and all other TLs are 0 mm then although the sum may be > 0 mm the calculation of TL response should be overwritten as a CR.

TL visit responses subsequent to CR

Only CR, PD or NE can follow a CR. If a CR has occurred, then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (i.e. 0 mm or < 10 mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met i.e. if a lymph node LD increases by 20% but remains < 10 mm.
- Step2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e. 0 mm or < 10 mm for lymph nodes) then response will be set to NE irrespective of whether, when referencing the sum of TL diameters, the criteria for PD are also met.
- Step 3: If not all lesions meet the CR criteria (i.e. a pathological lymph node selected as TL has short axis > 10 mm or the reappearance of previously disappeared lesion) or a new lesion appears, then response will be set to PD.
- Step 4: If after steps 1 – 3 a response can still not be determined the response will be set to remain as CR.

TL too big to measure

If a TL becomes too big to measure this should be indicated in the database and a size ('*x*') above which it cannot be accurately measured should be recorded. If using a value of *x* in the calculation of TL response would not give an overall visit response of PD, then this will be flagged and reviewed by the study team blinded to treatment assignment. It is expected that a visit response of PD will remain in the vast majority of cases.

TL too small to measure

If a TL becomes too small to measure, then this will be indicated as such on the case report form and a value of 5 mm will be entered into the database and used in TL calculations. However, a smaller value may be used if the radiologist has not indicated 'too small to measure' on the case report form and has entered a smaller value that can be reliably

measured. If a TL response of PD results (at a subsequent visit) then this will be reviewed by the study team blinded to treatment assignment.

Irradiated lesions/lesion intervention

Previously irradiated lesions (i.e. lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolization), should be handled in the following way. Once a lesion has had intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumours:

- Step 1: The diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD, this will remain as a valid response category.
- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and if ≤ 1/3 of the TLs have missing measurements then scale up as described in the 'Scaling' section below. If the scaling results in a visit response of PD then the patient would be assigned a TL response of PD.
- Step 3: If, after both steps, PD has not been assigned, then, if appropriate (i.e. if ≤ 1/3 of the TLs have missing measurements), the scaled sum of diameters calculated in step 2 should be used, and PR or SD then assigned as the visit response. Patients with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or < 10 mm for lymph nodes) and the lesions that have been subject to intervention have a value of 0 (or < 10 mm for lymph nodes) recorded. If scaling up is not appropriate due to too few non-missing measurements, then the visit response will be set as NE.

At subsequent visits, the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up (as per step 2 above).

Scaling (applicable only for irradiated lesions/lesion intervention)

If > 1/3 of TL measurements are missing (because of intervention) then the TL response will be NE, unless the sum of diameters of non-missing TL would result in PD (i.e. if using a value of 0 for missing lesions, the sum of diameters has still increased by 20% or more compared to nadir and the sum of TLs has increased by ≥ 5 mm from nadir).

If ≤ 1/3 of the TL measurements are missing (because of intervention) then the results will be scaled up (based on the sizes at the nadir visit to give an estimated sum of diameters) and this

will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions with missing measurements.

Example of scaling

Lesion 5 is missing at the follow-up visit; the nadir TL sum including lesions 1-5 was 74 mm.

The sum of lesions 1-4 at the follow-up is 68 mm. The sum of the corresponding lesions at the nadir visit is 62 mm.

Scale up as follows to give an estimated TL sum of 81 mm:

68 x 74 / 62 = 81 mm

CR will not be allowed as a TL response for visits where there is missing data. Only PR, SD or PD (or NE) could be assigned as the TL visit response in these cases. However, for visits with ≤ 1/3 lesion assessments not recorded, the scaled-up sum of TLs diameters will be included when defining the nadir value for the assessment of progression.

Lesions that split in two

If a TL splits in two, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge

If two TLs merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0cm.

Change in method of assessment of TLs

CT, MRI and clinical examination are the only methods of assessment that can be used within a trial, with CT and MRI being the preferred methods and clinical examination only used in special cases. If a change in method of assessment occurs, between CT and MRI this will be considered acceptable and no adjustment within the programming is needed.

If a change in method involves clinical examination (e.g. CT changes to clinical examination or vice versa), any affected lesions should be treated as missing.

3.1.2 Non-target lesions (NTLs) and new lesions - site investigator data

At each visit, the investigator should record an overall assessment of the NTL response. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

NTL response will be derived based on the investigator's overall assessment of NTLs as follows:

Table 4 NTL Visit Responses (RECIST v1.1)

Visit Responses	Description
Complete response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (< 10 mm short axis).
Progressive disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable (NA)	Only relevant if there are no NTLs at baseline.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit a determination of disease progression. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression, so the overall visit response will be PD irrespective of the TL and NTL response.

If the question 'Any new lesions since baseline' has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present but should not overtly affect the derivation.

Symptomatic progression is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs.

Patients with 'symptomatic progression' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

3.1.3 Overall RECIST v1.1 visit response - site investigator data

Table 5 below defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 5 RECIST v1.1 overall visit response

Target lesions	Non-target lesions	New lesions	Overall visit response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE or NA	No	PR
SD	Non-PD or NE or NA	No	SD
NA	Non-CR/Non-PD	No	SD (Non-CR/Non-PD [a])
NE	Non-PD or NE or NA	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD

Target lesions	Non-target lesions	New lesions	Overall visit response
Any	Any	Yes	PD

[a] Non-CR/Non-PD for overall response if only non-target lesions (no TLs) are present at baseline.

NOTE: An overall assessment of complete response (all other disease disappears/reverts to normal) would be changed to partial response if ascites remains present radiologically.

CR complete response; NA not applicable; NE not evaluable; PD progressive disease; PR partial response; (only relevant if there were no target lesions at baseline or no non-target lesions at baseline); SD stable disease; TL target lesion.

The following overall visit responses are possible depending on the extent of tumour disease at baseline:

- For patients with TLs (at baseline): CR, PR, SD, PD, or NE
- For patients with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE

Missing TL data

For a visit to be evaluable then all TL measurements should be recorded. However, a visit response of PD should still be assigned if any of the following occurred:

- A new lesion is recorded.
- An NTL visit response of PD is recorded.
- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5 mm, from nadir even assuming the non-recorded TLs have disappeared.

Note: the nadir can only be taken from assessments where all the TLs had a LD recorded.

If there is at least one TL measurement missing and a visit response of PD cannot be assigned, the visit response is NE.

If all TL measurements are missing, then the TL visit response is NE. Overall visit response will also be NE, unless there is a progression of non-TLs or new lesions, in which case the response will be PD.

3.1.4 Independent review

All radiological scans for all patients (including those at unscheduled visits, or outside visit windows) will be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging CRO (iCRO) for central analysis. A planned blinded independent central review (BICR) of all radiological imaging data for the patients at the discretion of AstraZeneca will be carried out

using RECIST version v1.1. The imaging scans will be reviewed by two independent radiologists using RECIST v1.1 and will be adjudicated, if required (i.e. two reviewers' review the scans and adjudication is performed by a separate reviewer in case of a disagreement). For each patient, the BICR will define the overall visit response (i.e. the response obtained overall at each visit by assessing TLs, NTLs and new lesions) data and no programmatic derivation of visit response is necessary. (For patients with TLs at baseline: CR, PR, SD, PD, NE; for patients with NTLs only: CR, SD, PD, NE; for patients with no disease identified at baseline: PD, no evidence of disease [NED], NE). If a patient has had a tumour assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression in which case the response will be assigned as PD). RECIST assessments/scans contributing towards a particular visit may be performed on different dates and for the central review the date of progression for each reviewer will be provided based on the earliest of the scan dates of the component that triggered the progression.

If adjudication is performed, the reviewer that the adjudicator agreed with will be selected as a single reviewer (note in the case of more than one review period, the latest adjudicator decision will be used). In the absence of adjudication, the records for all visits for a single reviewer will be used. The reviewer selected in the absence of adjudication will be the reviewer who read the baseline scan first. The records from the single selected reviewer will be used to report all BICR RECIST v1.1 information including dates of progression, visit response, censoring and changes in target lesion dimensions.

Results of this independent review will not be communicated to investigators and the management of patients will be based solely upon the results of the RECIST v1.1 assessment conducted by the investigator.

A BICR in the overall population and in the *PIK3CA/AKT1/PTEN*-altered population will be performed for the primary PFS analysis database lock which will cover all of the scans up to the data lock.

Further details of the BICR will be documented in the Independent Review Charter (IRC).

3.2 Efficacy Variables

3.2.1 Progression-free survival (PFS)

PFS is defined as the time from the date of randomisation until the date of objective disease progression, as defined by RECIST v1.1, or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy prior to progression (i.e., date of PFS event or censoring – date of randomisation + 1). PFS will be assessed by investigator assessment. A sensitivity analysis of PFS by BICR will be reported.

If the patient progresses or dies immediately after two or more consecutive missed visits, the patient will be censored at the time of the latest evaluable RECIST v1.1 assessment prior to the two missed visits. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment.

Given the scheduled visit assessment scheme (every 8 weeks (±7 days) for the first 78 weeks (18 months) and every 12 weeks (±7 days) thereafter, from randomisation to radiological progression) the definition of 2 missed visits will change.

- If the previous RECIST assessment is < = study day 455 (i.e. end of week 65) then two missing visits will equate to 18 weeks since the previous RECIST assessment, allowing for early and late visits (i.e. 2 x 8 weeks + 1 week for an early assessment + 1 week for a late assessment = 18 weeks).
- If the two missed visits occur over the period when the scheduled frequency of RECIST assessments changes from every 8 weeks to every 12 weeks this will equate to 22 weeks (i.e. take the average of 8 and 12 weeks which gives 10 weeks and then apply same rationale, hence 2 x 10 weeks + 1 week for an early assessment + 1 week for a late assessment = 22 weeks). The time period for the previous RECIST assessment will be from study days 456 to 553 (i.e. start of week 66 to end of week 79).
- From start of week 80 (day 554) onwards (when the scheduling changes to twelve-weekly assessments), two missing visits will equate to 26 weeks (i.e. 2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment = 26 weeks).

If the patient has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of baseline, then they will be treated as an event with date of death as the event date.

The PFS time will always be derived based on scan/assessment dates and not on visit dates.

RECIST v1.1 assessments/scans contributing toward a particular visit may be performed on different dates. The following rules will be applied:

- For investigator assessments, the date of progression will be determined based on the
  earliest of the RECIST v1.1 assessment/scan dates of the component that indicates progression.

- For BICR assessments, the date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression for the adjudicated reviewer selecting PD or of the reviewer who read baseline first if there is no adjudication for BICR data.
- For both BICR and investigational assessments when censoring a patient for PFS, the patient will be censored at the latest of the scan dates contributing to a particular overall visit assessment.

Note: for TLs only, the latest scan date is recorded out of all scans performed at that assessment for the TLs and similarly for NTLs only the latest scan date is recorded out of all scans performed at that assessment for the NTLs.

3.2.2 Overall survival (OS)

Overall survival is defined as the time from the date of randomisation until death due to any cause regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy (i.e. date of death or censoring – date of randomisation + 1). Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive (SUR_DAT, recorded within the Survival Status eCRF page).

Assessments for survival will be conducted every 8 weeks for the first 2 years following objective disease progression or treatment discontinuation and then every 12 weeks.

Survival information may be obtained via telephone contact with the patient, patient's family, by contact with the patient's current physician, or local death registries as described in Protocol Section 7.3.

Note: Survival calls will be made in the week following the date of data cut-off (DCO) for the analysis, and if patients are confirmed to be alive or if the death date is post, the DCO date these patients will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the final OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly-available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

Note: For any OS analysis performed, it may be necessary to use all relevant CRF fields to determine the last recorded date on which the patient was known to be alive. The last date for

each individual patient is defined as the latest among the following dates recorded on the case report forms (CRFs):

- AE start and stop dates
- Admission and discharge dates of hospitalisation
- Study treatment date
- End of treatment date
- Laboratory test dates
- Date of vital signs
- Disease assessment dates on Tumour Evaluation pages
- Start and stop dates of alternative anticancer treatment
- Date last known alive on survival status CRF
- End of study date

If a patient is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided:

a. For missing day only – using the 1st of the month

b. For missing day and month – using the 1st of January

If there is evidence of death but the date is entirely missing, it will be treated as missing, i.e., censored at the last known alive date.

3.2.3 Progression free survival 2 (PFS2)

Time from randomisation to second progression or death (PFS2) will be defined as the time from date of randomisation to the earliest of the progression event (following the initial progression), subsequent to the first subsequent therapy or death.

Following discontinuation of study treatment due to disease progression, as determined by investigator-based by RECIST v1.1 assessment, patients who started on subsequent cancer therapy post progression will continue to be followed at the 30-day follow-up visit, every 8 weeks (±7 days) for the first 2 years, and every 12 weeks (±7 days) thereafter for documentation of progression on second-line therapy. Determination of progressive disease for PFS2 will be by institutional call.

Patients alive and for whom a second disease progression has not been observed should be censored at the date last known alive and without a second disease progression (i.e. censored

at the PFS or PFS2 assessment date, whichever is later, if the patient has not had a second progression or death).

3.2.4 Objective response rate (ORR)

The secondary outcome ORR is defined as the percentage of patients with at least one investigator-assessed visit response of CR or PR (as assessed by the investigator, using RECIST v1.1) and will be based on a subset of patients with measurable disease at baseline per the site investigator. ORR will also be defined using the BICR data to define a visit response of CR or PR, with the denominator defined as subset of all randomised patients with measurable disease at baseline per BICR.

Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue randomised treatment without progression, receive a subsequent anticancer therapy (note that for this analysis radiotherapy is not considered a subsequent anticancer therapy) and then respond will not be included as responders in the ORR.

Best objective response (BoR)

Best objective response (BoR) is calculated based on the overall visit responses from each tumour assessment, described in Section 3.1.3. It is the best response a patient has had following randomisation, but prior to starting any subsequent cancer therapy and up to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression. Categorisation of BoR will be based on RECIST using the following response categories: CR, PR, SD, PD and NE.

For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 8 weeks minus 1 week, i.e. at least 49 days (to allow for an early assessment within the assessment window), after randomisation. For CR/PR, the initial overall visit assessment that showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

BoR will be determined programmatically based on RECIST from the overall visit response using all investigator assessment data up until the first progression event. It will also be determined programmatically based on RECIST using all site investigator data up until the first progression event.

For patients whose progression event is death, BoR will be calculated based upon all evaluable RECIST assessments prior to death.

For patients who die with no evaluable RECIST assessments, if the death occurs ≤17 weeks (i.e. 16 weeks + 1 week to allow for a late assessment within the assessment window) after randomisation, then BoR will be assigned to the progression (PD) category. For patients who

die with no evaluable RECIST assessments, if the death occurs >17 weeks after randomisation then BoR will be assigned to the NE category.

A patient will be classified as a responder if the RECIST criteria for a CR or PR are satisfied at any time following randomisation, prior to RECIST progression and prior to starting any subsequent cancer therapy.

ORR based on responses confirmed in the subsequent visit may be required.

Confirmed response

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 7 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit.

3.2.5 Duration of response (DoR)

The secondary outcome DoR (per RECIST v1.1 using Investigator assessment) will be defined for patients with CR or PR as the time from the date of first documented response until date of documented progression or death in the absence of disease progression (i.e. date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR as defined by Table 5.

If a patient does not progress following a response, then their DoR will use the PFS censoring time.

3.2.6 Clinical benefit rate (CBR)

Clinical benefit rate at 24 weeks is defined as the percentage of patients who have one of the following:

1. A BoR of CR without subsequent therapy or
2. A PR without subsequent therapy
3. or who have SD for at least 23 weeks without subsequent therapy after start of treatment (to allow for an early assessment within the assessment window).

Duration of SD is defined as: (date last evaluable assessment of SD - randomisation date +1 in days). SD after the start of subsequent cancer therapy should not be included in this duration.

Patients without a post-baseline tumour assessment are considered to have no clinical benefit.

3.2.7 Time to first subsequent chemotherapy or death (TFSC)

As a supportive summary to PFS, time to first subsequent chemotherapy or death (TFSC) is defined as the time from the date of randomisation to the earlier of start date of the first subsequent chemotherapy after discontinuation of randomised treatment, or death (i.e. date of first subsequent chemotherapy/death or censoring – date of randomisation + 1). Patients alive and not known to have had a first subsequent chemotherapy will be censored at the earliest of: date of study termination, date last known alive, DCO or, the last date that the patient was known not to have received a first subsequent chemotherapy (obtained from the case report forms CAPRX1 and TTSCAPRX).

3.2.8 Time to definitive deterioration of the ECOG performance status

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. Deterioration is defined as a 1-point increase in ECOG score from baseline, and the deterioration is considered definitive if no improvements in the ECOG performance status are observed at a subsequent time of measurement during the treatment period (within 30 + 7 days after the last dose of study treatment), or if there are no further assessments following the time point where the deterioration is observed.

Patients who have not had definitive deterioration and did not die at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable ECOG assessment. However, if the patient has definitive deterioration or dies immediately after two or more consecutive missed visits, the patient will be censored at the time of the latest evaluable ECOG assessment prior to the two missed visits.

Given the scheduled visit assessment scheme (every 2 weeks (-1/+3 days) for the first 8 weeks (2 cycles) and every 4 weeks (-1/+3 days) thereafter, from randomisation to treatment discontinuation) the definition of 2 missed visits will change.

- If the previous ECOG assessment is before or on study day 31 (i.e. end of week 4 + 3 days) then two missing visits will equate to 32 days since the previous ECOG assessment, allowing for early and late visits (i.e. 2 x 14 days + 1 day for an early assessment + 3 days for a late assessment = 32 days).
- If the two missed visits occur over the period when the scheduled frequency of ECOG assessments changes from every 2 weeks to every 4 weeks this will equate to 46 days (i.e. take the average of 2 and 4 weeks which gives 3 weeks and then apply same rationale, hence 2 x 21 days + 1 day for an early assessment + 3 days for a late assessment = 46 days). The time period for the previous ECOG assessment will be from study days 32 to 55 (i.e. end of week 4 + 4 days to end of week 8 – 1 day).

- From end of week 8 (day 56) onwards (when the scheduling changes to four-weekly assessments), two missing visits will equate to 60 days (i.e. 2 x 28 days + 1 day for an early assessment + 3 days for a late assessment = 60 days).

3.3 Patient reported outcome (PRO) variables

The following PRO questionnaires will be used to assess the patient experience, including global health status/health-related quality of life (HRQoL), functioning and symptoms: EORTC QLQ-C30 with the EORTC QLQ-BR23 breast cancer specific module, PGIS, PGIC, PGI-TT, PRO-CTCAE and EQ-5D-5L. All items/questionnaires will be scored according to published guidelines or the developer's guidelines, if published guidelines are not available as described in the sections below. PRO analyses will be based on the FAS and Altered Subgroup FAS, unless stated otherwise. The PRO-CTCAE and PGI-TT will be based on the Safety and Altered Safety Analysis Set.

The PRO evaluations will be separated by on-treatment assessments (those taken on or before last dose of study treatment) and follow-up assessments (those taken after last dose of study treatment).

Descriptive summaries for absolute changes from baseline and summaries of response by visit will be reported for all on-treatment visits and follow-up visits.

Formal analysis of change from baseline using a mixed model repeated measures (MMRM) will only include on-treatment visits.

All available on-treatment and off-treatment PRO assessments will be used to determine time to deterioration.

The main PRO measures identified in the secondary objectives are global health status/QoL, physical function, role function, fatigue, pain and appetite loss subscales of the EORTC QLQ-C30. However, separate analysis will be conducted for each EORTC QLQ-C30 and EORTC QLQ-BR23 scale/symptom score unless stated otherwise. Prioritized subscales (health status/QoL, physical function, role function, fatigue, pain, and appetite loss) reflect feedback on the PRO strategy from the US Food and Drug Administration (FDA).

3.3.1 EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), and 2-item global health status/QoL scale, along with 5 individual item symptom scores (appetite loss, dyspnoea, insomnia, constipation, and diarrhoea). The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 Scoring Manual (Fayers et al. 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/scores, each of the functional scales, and the global measure of health status

scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global measure of health status and functional scales indicate better health status/function, whereas higher scores on symptom scales/scores represent greater symptom severity. The EORTC QLQ-C30 functional and symptom scales, individual symptom items and global health status are derived as follows (Fayers et al. 2001):

1. Calculate the average of the items that contribute to the scale or take the value of an individual item, i.e. the raw score (RS):

   $$RS = (I_1 + I_2 + \ldots + I_n) / n,$$

   where $I_1 + I_2 + \ldots + I_n$ are the items included in a scale and n is the number of items in a scale.

2. Use a linear transformation to standardize the raw score, so that scores range from 0 to 100, where a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

   Functional scales: $Score = (1 - [RS - 1] / range) * 100$

   Symptom scales/items; global health status: $Score = ([RS - 1] / range) * 100,$

   where *range* is the difference between the maximum and the minimum possible value of RS.

For each subscale, if < 50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items (Fayers et al. 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded.

The number of items and item range for each scale/item are displayed in Table 6 below.

Table 6 EORTC QLQ-C30 scales and scores

Scale/ item	Scale/ item abbreviation	Number of items (n)	Item range	Item numbers
Global health status/ QoL	QL	2	6	29, 30
Functional scales				
Physical	PF	5	3	1-5
Role	RF	2	3	6, 7
Cognitive	CF	2	3	20, 25
Emotional	EF	4	3	21-24
Social	SF	2	3	26, 27

Scale/ item	Scale/ item abbreviation	Number of items (n)	Item range	Item numbers
Symptom scales				
Fatigue	FA	3	3	10, 12, 18
Pain	PA	2	3	9, 19
Nausea/ vomiting	NV	2	3	14, 15
Symptom items				
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhoea	DI	1	3	17

EORTC European Organisation for Research and Treatment of Cancer; QLQ-C30 30-item core quality-of-life questionnaire. Financial difficulties" (i.e., item 28) was not collected.

Definition of clinically meaningful changes - visit response

Changes in score compared with baseline will be evaluated. A clinically meaningful change is defined as an absolute change in the score from baseline of ≥ 10 for scales from the EORTC QLQ-C30 (Osoba et al. 1998). For example, a clinically meaningful improvement in physical function (as assessed by EORTC QLQ-C30) is defined as an increase in the score from baseline of ≥ 10, whereas a clinically meaningful deterioration is defined as a decrease in the score from baseline of ≥ 10.

At each post-baseline assessment, the change in global health status/QoL, symptoms, and functioning score from baseline will be categorised as improvement, no change, or deterioration for each patient as shown in Table 7.

Table 7 Mean change and clinically meaningful change – EORTC QLQ-C30

Score	Change from baseline	Visit response
EORTC QLQ-C30 global quality-of-life score	≥ +10 (increase of at least 10)	Improvement
	≤ -10 (decrease of at least 10)	Deterioration
	Otherwise	No change
	≥ +10 (increase of at least 10)	Deterioration

Score	Change from baseline	Visit response
EORTC QLQ-C30 symptom scales	≤ -10 (decrease of at least 10)	Improvement
	Otherwise	No change
EORTC QLQ-C30 functional scales	≥ +10 (increase of at least 10)	Improvement
	≤ -10 (decrease of at least 10)	Deterioration
	Otherwise	No change

EORTC European Organisation for Research and Treatment of Cancer; QLQ-C30 30-item core quality-of-life questionnaire.

The denominator for each visit will be a subset of the FAS with an evaluable baseline and an evaluable score at the visit.

Time to deterioration EORTC QLQ-C30

Time to definitive HRQoL, physical function, role function, and symptom scales (fatigue, pain and appetite loss) deterioration will be defined as the time from the date of randomisation until the date of the first clinically meaningful deterioration (as defined in Table 7) with a sustained clinically meaningful deterioration at all subsequent time points prior to the end of follow-up, or death, whichever is earliest.

Patients with no evaluable baseline assessment or baseline score < 10 for QoL/function or baseline score > 90 for symptoms will be excluded from the analysis.

All missing visits after the first clinically meaningful deterioration visit will be ignored for the evaluation of the definitive HRQoL, physical function and symptom deterioration event.

Patients with no definitive deterioration prior to the end of follow-up or death will be censored at the last available PRO assessment (for the corresponding item/scale).

Patients whose global health status/HRQoL, physical function, role function, or symptom scale (pain, fatigue, and appetite loss) scores have not shown a clinically meaningful deterioration prior to the end of follow-up, or death will be censored at the time of their last PRO assessment (for the corresponding item/scale). Also, if global health status/HRQoL, physical function, role function, or symptom scale (pain, fatigue, and appetite loss) score deteriorates after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment, where the overall score response could be evaluated prior to the 2 missed visits.

If the patient has no evaluable post baseline PRO assessment they will be censored at Day 1. The censoring rules are summarised in Table 8.

Table 8 Censoring rules for time to deterioration (symptoms, physical function, global health status/ QoL)

Status	Date of censoring
No evaluable post baseline PRO assessment	Randomisation date
No evaluable baseline assessments or baseline score < 10 for QoL/function or baseline score > 90 for symptoms	Excluded from analysis
No clinically meaningful deterioration regardless of alive/death at time of analysis	Last available PRO assessment
Deterioration or death after 2 or more missed PRO visits	Last available PRO assessment prior to the 2 missed visits

PRO Patient reported outcome, QoL Quality of Life.

3.3.2 EORTC QLQ-BR23

The EORTC QLQ-BR23 is a validated breast cancer-specific module used in conjunction with the core QLQ-C30 to assess breast cancer-specific HRQoL (Sprangers et al 1996). The self-administered instrument includes 23-items and yields 5 multi-item scores (body image, sexual functioning, arm symptoms, breast symptoms, and systemic therapy side effects). Items are scored on a 4-point verbal rating scale: "Not at All," "A Little," "Quite a Bit," and "Very Much". Scores are transformed to a 0 to 100 scale, the same way as specified for EORTC QLQ-C30 in Section 3.3.1, where higher scores indicate better functioning, better HRQoL, or greater level of symptom. For missing subscale items or missing single items the same rules as specified in Section 3.3.1 will apply.

The number of items and item range for each scale/item are displayed in Table 9.

Table 9 EORTC QLQ-BR23 scales/scores

Scale/ item	Scale/ item abbreviation	Number of items (n)	Item range	Item numbers
Functional scales				
Body image	BRBI	4	3	39-42
Sexual functioning	BRSEF	2	3	44, 45
Sexual enjoyment	BRSEE	1	3	46
Future perspective	BRFU	1	3	43

Symptom scales				
Systemic therapy side effects	BRST	7	3	31-34, 36, 37, 38
Breast symptoms	BRBS	4	3	50-53
Arm symptoms	BRAS	3	3	47, 48, 49
Upset by hair loss	BRHL	1	3	35

EORTC European Organisation for Research and Treatment of Cancer; QLQ-BR23 Quality of Life Questionnaire breast cancer specific module.

Changes in score compared with baseline will be evaluated. A clinically meaningful change is defined as an absolute change in the score from baseline of ≥ 10 for scales/items from QLQ-BR23. For example, a clinically meaningful deterioration or worsening in breast symptoms (as assessed by QLQ-BR23) is defined as an increase in the score from baseline of ≥ 10. At each post baseline assessment, the change in symptom score from baseline will be categorised as improvement, no change, or deterioration, as shown in Table 10.

Table 10 Mean change and clinically meaningful change – EORTC QLQ-BR23

Score	Change from baseline	Visit response
QLQ-BR23 functional scales and items	≥ +10 (increase of at least 10)	Improvement
	≤ -10 (decrease of at least 10)	Deterioration
	Otherwise	No change
QLQ-BR23 symptom scales and items	≥ +10 (increase of at least 10)	Deterioration
	≤ -10 (decrease of at least 10)	Improvement
	Otherwise	No change

EORTC European Organisation for Research and Treatment of Cancer; QLQ-BR23 Quality of Life Questionnaire breast cancer specific module.

The denominator for each visit will be a subset of the FAS with an evaluable baseline and an evaluable score at the visit.

Time to deterioration EORTC QLQ-BR23

Time to definitive deterioration will be defined as the time from the date of randomisation until the date of the first clinically meaningful deterioration (as defined in Table 10) with a sustained clinically meaningful deterioration at all subsequent time points prior to the end of follow-up, or death, whichever is earliest.

Patients with no evaluable baseline assessment or baseline score < 10 for function or baseline score > 90 for symptoms will be excluded from the analysis.

All missing visits after the first clinically meaningful deterioration visit will be ignored for the evaluation of the definitive deterioration event.

Patients with no definitive deterioration prior to the end of follow-up or death will be censored at the last available PRO assessment (for the corresponding item/scale).

Patients whose functional or symptoms scores have not shown a clinically meaningful deterioration prior to the end of follow-up, or death will be censored at the time of their last PRO assessment (for the corresponding item/scale). Also, if functional or symptom score deteriorates after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment, where the overall score response could be evaluated prior to the 2 missed visits.

If the patient has no evaluable post baseline PRO assessment they will be censored at Day 1. The censoring rules are summarised in table below.

Table 11 Censoring rules for time to deterioration EORTC QLQ-BR23

Status	Date of censoring
No evaluable post baseline PRO assessment	Randomisation date
No evaluable baseline assessments or baseline score < 10 for functional score or baseline score > 90 for symptoms score	Excluded from analysis
No clinically meaningful deterioration regardless of alive/death at time of analysis	Last available PRO assessment
Deterioration or death after 2 or more missed PRO visits	Last available PRO assessment prior to the 2 missed visits

PRO Patient reported outcome.

3.3.3 Patient reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE)

The patient reported outcomes version of the common criteria for adverse events (PRO-CTCAE), a PRO version of the CTCAE system developed by the National Cancer Institute (NCI), is included to assess tolerability from the patient's perspective. It was developed in recognition that collecting symptom data directly from patients can improve the accuracy and efficiency of symptomatic AE data collection. Symptoms have been converted to patient terms (e.g., CTCAE term "myalgia" converted to "aching muscles"). Items capture the presence, frequency, severity and/or interference with usual activities, depending on the AE. Five items that are considered relevant for the trial were selected (CSP Appendix I). For each question, patients select the value that best describes their experience over the past week.

3.3.4 Patient global impression - severity (PGIS)

The PGIS is a single item included to assess how a patient perceives their overall severity of cancer symptoms over the past week. The response options of the PGIS are scored using a 6-point scale: 1 = No Symptoms; 2 = Very Mild; 3 = Mild; 4 = Moderate; 5 = Severe; 6 = Very Severe.

3.3.5 Patient global impression - change (PGIC)

The PGIC is a single item included to assess how a patient perceives his or her overall change in health status since the start of study treatment. The response options for the PGIC are as follows: Much Better (+3), Moderately Better (+2), A Little Better (+1), About the Same (0), A Little Worse (-1), Moderately Worse (-2), and Much Worse (-3).

3.3.6 Patient global impression-treatment tolerability (PGI-TT)

The PGI-TT is a single item included to assess how a patient perceives the overall tolerability of the study treatment. The response options for the PGI-TT are as follows: Not at all (1), A little bit (2), Somewhat (3), Quite a bit (4) and Very much (5).

3.3.7 EQ-5D-5L

The EQ-5D-5L will be used to explore the impact of treatment and disease state on health state utility.

The EQ-5D-5L, developed by the EuroQol Group, is a generic questionnaire that provides a simple descriptive profile of health and a single index value for health status for economic appraisal. The EQ-5D-5L questionnaire comprises six questions that cover five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible five options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/ extreme problems). A unique EQ-5D health state, termed the EQ-5D-5L profile, is reported as a five-digit code with a possible 3,125 health states. For example, state 11111 indicates no problems on any of the five dimensions. Respondents also assess their health today using the EQ-VAS (visual analogue scale), which ranges from 0 (worst imaginable health) to 100 (best imaginable health).

The EQ-5D profile will be converted into a weighted health state utility value, termed the EQ-5D index, by applying a country-specific equation to the EQ-5D-5L profile that represents the comparative value of health states. This equation is based on national valuation sets elicited from the general population and the base case will be the UK perspective. Where a valuation set has not been published, the EQ-5D-5L profile will be converted to the EQ-5D

index using a crosswalk algorithm (van Hout et al. 2012). Further details regarding the evaluation of EQ-5D-5L will be presented in the payer analyses plan (PAP).

The evaluable population will be the FAS.

3.3.8 Compliance

Summary measures of compliance over time will be derived for EORTC QLQ-C30, PRO-CTCAE, PGI-TT, EORTC QLQ-BR23 and EQ-5D-5L, respectively. These will be based upon:

- Received questionnaire: A questionnaire that has been received and has a completion date and at least one individual item completed.
- Expected questionnaire: A questionnaire that is expected to be completed at a scheduled assessment time e.g., a questionnaire from a patient who has not withdrawn from the study at the scheduled assessment time but excluding patients in countries with no available translation. Date of study discontinuation will be mapped to the nearest visit date to define the number of expected forms. PGI-TT and PRO-CTCAE questionnaires are expected until 4 weeks post discontinuation of study treatment.
- Evaluable questionnaire: A questionnaire with a completion date and at least one subscale that is non-missing.

Compliance over time will be calculated separately for each visit, including baseline, as the number of patients with an evaluable questionnaire at the time point (as defined above), divided by number of patients still expected to complete questionnaires. Similarly, the evaluability rate over time will be calculated separately for each visit, including baseline, as the number of evaluable questionnaires (per definition above), divided by the number of received questionnaires.

For compliance over time, all visits (including follow-up visits) with at least 20 patients in each of the treatment arms will be reported.

3.4 Health care resource use variables

To investigate the impact of treatment and disease on health care resource, the following variables will be captured:

- Planned and unplanned hospital attendances beyond trial protocol mandated visits (including physician visits, emergency room visits, day cases and admissions).
- Primary sign or symptom the patient presents with.
- Length of hospital stay.
- Length of any time spent in an intensive care unit (ICU).

Where admitted overnight, the length of hospital stay will be calculated as the difference between the date of hospital discharge (or death date) and the start date of hospitalisation or start of study drug if the start of study drug is after start date of hospitalisation (length of hospital stay = end date of hospitalisation – start date of hospitalisation + 1). Patients with missing discharge dates will be calculated as the difference between the last day with available data and the start date of hospitalisation. The length of ICU stay will be calculated using the same method.

3.5 Safety Variables

Safety and tolerability will be assessed in terms of adverse events (AEs) [including serious adverse events (SAEs)], deaths, physical examinations, laboratory findings, WHO/ECOG PS, vital signs, electrocardiograms (ECGs) and exposure, which will be collected for all patients.

Data from all cycles of treatment will be combined in the presentation of safety. The safety analysis set will be used for reporting of safety data, apart from deaths, which are reported for FAS.

3.5.1 Exposure and dose interruptions

3.5.1.1 Treatment exposure for capivasertib or placebo

As capivasertib/placebo is dosed 400 mg (2 tablets) BD given on an intermittent weekly dosing schedule, patients will be dosed on Days 1 to 4 in each week of a 28-day treatment cycle and Fulvestrant is given 500 mg (2 injections) on Day 1 of Weeks 1 and 3 of Cycle 1, and then on Day 1, Week 1 of each cycle thereafter.

Total (or intended) exposure

The total (or intended) exposure (i.e. duration of treatment) of a patient to capivasertib/placebo is calculated using the start and stop dates of capivasertib/placebo and the intended dosing interval. For a dosing period of capivasertib/placebo, the total (or intended) exposure is calculated as the number of days from date A to date B (i.e. B-A+1) where

- A is the date of first dose of capivasertib/placebo in the dosing period.
- B is the earliest of
    - the date when the last non-zero dose of capivasertib/placebo was received
    - the date of capivasertib/placebo discontinuation
    - if capivasertib/placebo has not been permanently discontinued, then DCO date
    - the date of death

Total (or intended) exposure (months) of Capivasertib or placebo: = (date of last dose where dose > 0 – first dose date +1) /(365.25/12). A cycle will be counted if the treatment is started even if the full dose is not delivered.

Actual exposure

Actual exposure of Capivasertib or placebo = intended exposure – total duration of dose interruptions, where the total duration of dose interruption is defined as any length of time where the patient has not taken any of the planned doses.

The actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

Number of treatment cycles received

Exposure will also be measured by the number of cycles received. A cycle corresponds to a period of 28 days. If a cycle is prolonged due to toxicity, this should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered.

Missed or forgotten doses

Missed and forgotten doses should be recorded on the DOSE module as a dose interruption with the reason recorded as "Subject forgot to take dose". These missed or forgotten doses will not be included as dose interruptions in the summary tables, but the information will appear in the listing for dosing. However, these missed and forgotten doses will be considered in the derivation of actual exposure.

3.5.1.2 Treatment exposure for Fulvestrant

Total (or intended) exposure

The total (or intended) exposure (i.e. duration of treatment) of a patient to fulvestrant is calculated using the start and stop dates of fulvestrant and the intended dosing interval. For a dosing period of fulvestrant, the total (or intended) exposure is calculated as the number of days from date A to date B (i.e. B-A+1) where

- A is the date of first dose of fulvestrant in the dosing period.
- B is the earliest of:
    - the date of death,
    - the date of DCO, and
    - the date when the last non-zero dose of fulvestrant was received plus D, where D is equal to the scheduled number of days between doses minus one. D will take value as specified below for fulvestrant treatment to account for the completion of full cycle period.
        - If the last fulvestrant dose is on cycle 1, then D = 13
        - If the last fulvestrant dose is on cycle 2 or onwards, then D = 27

Total (or intended) exposure (months) of fulvestrant: = (min(date of last dose where dose > 0 + D, date of death, date of DCO) – first dose date +1) /(365.25/12).

Actual exposure

Exposure will be measured by the number of cycles received. A cycle corresponds to a period of 28 days. If a cycle is prolonged due to toxicity, this should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered.

3.5.2 Dose intensity

Dose intensity will be derived for study treatment capivasertib/placebo and fulvestrant, separately. Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. RDI will be defined as follows:

- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the day of treatment discontinuation. D is the total dose that would be delivered, if there were no modification to dose or schedule: For example, if capivasertib/placebo have been administered as scheduled for 4 complete cycles, D = 400 mg * 2 doses per day * 4 days per week* 4 weeks * 4 cycles. For fulvestrant, D = 500 mg * 2 for Cycle 1 + 500 mg * number of cycles for cycle 2 onwards.

If a patient discontinues during a cycle, then only count the intended doses up to that day.

Number of intended doses is derived by counting 2 doses per day times 4 days per week times 4 weeks per cycle (32 doses per cycle) up to discontinuation of capivasertib or placebo and 1 injection/dose on weeks 1, 3 of cycle 1 and week 1 from cycle 2 onwards up to discontinuation of fulvestrant.

3.5.3 Safety endpoints supporting the dose

The following safety endpoints of interest will be derived, using the first dose of capivasertib or placebo as the reference date:

- time to first dose modification of capivasertib/placebo due to an AE
- time to first dose reduction of capivasertib/placebo due to an AE
- time to first dose interruption of capivasertib/placebo due to an AE
- time to capivasertib/placebo discontinuation due to an AE

3.5.4 Adverse events

AEs and SAEs will be collected throughout the study, from date of informed consent until 30 days after the last dose of study treatment. For this study, on treatment will be defined as the time between date of the first dose of study treatment (capivasertib, placebo or fulvestrant) and 30 days (+ 7-day window) following the last dose of study treatment. If an event starts

outside of this period and it is considered possible that it is due to late onset toxicity to study drug, then it should be reported as an AE or SAE. Pre-treatment AEs will be defined as any AEs occurring before randomised treatment (i.e. before the administration of the first dose on Study Day 1).

Treatment emergent AEs (TEAEs) will be defined as any AEs that started after the first dose of study treatment or that started prior to dosing and worsened during on treatment period (by investigator report of a change in intensity) following exposure to treatment. If an AE is not worse than the baseline (pre-dose) severity, then it will not be classified as a TEAE.

The Medical Dictionary for Regulatory Activities (MedDRA) [using v23.0 or later] will be used to code AEs. AEs will be graded according to the National Cancer Institute (NCI) common terminology criteria for adverse event (CTCAE) version 5.0. The CTCAE grade will be assigned by the investigator as follows:

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening or disabling AE
- Grade 5: Death related to AE

Missing start and stop dates for AEs will be handled using the rules described in Section 3.5.14.3. AEs that have missing causality (after data querying) will be assumed to be related to capivasertib/placebo only.

3.5.5 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and 'Discontinuation of Investigational Product due to Adverse Events' (DAEs). Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

3.5.6 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) are events of scientific and medical interest specific to understanding of the capivasertib safety profile and require close monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or non-serious.

AESI for capivasertib will be listed before database lock (DBL) and documented in the Trial Master File.

3.5.7 Laboratory measurements

Laboratory data will be collected throughout the study as described in the Schedule of Assessments (SoA, Appendix A). Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be collected as described in Section 8.2.1 of the CSP.

For the derivation of baseline and post baseline visit values, the rules described in Section 3.5.13.1 of this document considering definition of baseline, visit windows and how to handle multiple records will be used.

Change from baseline in haematology and clinical chemistry variables, also including percent change from baseline for HbA1C, will be calculated for each post-dose visit on treatment. CTCAE grades will be defined at each visit according to the CTCAE grade criteria using local or project ranges as required, after conversion of lab result to corresponding AstraZeneca preferred units. The following parameters have CTCAE grades defined for both high and low values: glucose, haemoglobin, lymphocytes, potassium, sodium, magnesium and corrected calcium. For these parameters high and low CTCAE grades will be calculated.

Albumin-corrected calcium product will be derived during creation of the reporting database using the following formula:

Albumin-corrected calcium (mmol/L) = Total calcium (mmol/L) +([40 – albumin (G/L)] x 0.02)

Absolute values will be compared to the project reference range and classified as low (below range), normal (within range or limits of range) and high (above range).

The maximum or minimum on treatment value (depending on the direction of an adverse effect) will be defined for each laboratory parameter as the maximum (or minimum) post-dose value at any time, including unscheduled and repeat visits.

Project reference ranges will be used throughout for reporting purposes. If the project range is unavailable for a particular test, local ranges will be used. The denominator used in laboratory summaries of CTCAE grades will only include evaluable patients (i.e., those who had sufficient data to have the possibility of an abnormality). For example,

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded.
- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient needs only to have 1 post dose-value recorded.

Situations in which laboratory results should be reported as AEs are described in Section 8.3.7 of the CSP.

3.5.8 Vital signs

Vital signs will be assessed at screening and timelines as specified in the SoA (Appendix A). The following vital signs will be measured as described in Section 8.2.3 of the CSP: Systolic and diastolic blood pressure, pulse rate, respiratory rate, weight and body temperature.

For the derivation of baseline and post-baseline visit values, the definitions and rules described in Section 3.5.13 for visit windows, and how to handle multiple records will be used.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.7 of the CSP.

3.5.9 Physical examinations

Physical examinations will be performed at screening and timelines as specified in the SoA (Appendix A) and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems.

Weight and height will be assessed at timelines as specified in the SoA (Appendix A).

Abnormalities recorded prior to the first dose of study treatment will be recorded as part of the patient's baseline signs and symptoms. New clinically relevant abnormalities first recorded after first dose of study treatment will be recorded as AEs unless unequivocally related to the disease under study. Situations in which physical examination results should be reported as AEs are described in Section 8.3.7 of the CSP.

3.5.10 Electrocardiograms (ECGs) and Echocardiograms (ECHOs)

Triplicate 12-lead ECG will be recorded at screening and as per scheduled assessment throughout the study as described in Section 1.1 and 8.2.4 of the CSP.

ECHO (LVEF) will be recorded at screening and as clinically indicated throughout the study as described in Section 1.1 and 8.2.5 of the CSP. For patients from VHP countries only post baseline ECHO (LVEF) data will be recorded as per scheduled assessment every 12 weeks.

All ECGs to be conducted as triplicate measurements, within approximately 5 minutes of starting (the 3 ECGs separated by approximately 2 minutes). Assessments should be performed as close as possible to, but within 30 minutes of the nominal time point. Baseline

and post baseline values will be derived as average of assessments collected using triplicate measurements.

The following ECG variables will be collected: ECG PR interval, QRS duration, QT interval, RR interval and overall ECG evaluation.

The overall evaluation of an ECG will either be "normal" or "abnormal" with abnormalities categorised as either "clinically significant" or "not clinically significant". If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition.

The QT interval corrected for heart rate using Fridericia's correction (QTcF) will be calculated in the eCRF as follows (where QT and RR are in seconds):

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Situations in which ECG results should be reported as AEs are described in Section 8.3.7 of the CSP.

QTcF will also be conducted as triplicate measurements. Baseline and post baseline values will be derived as average of assessments collected using triplicate measurements.

3.5.11 World Health Organisation (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status (PS)

The WHO/ECOG PS scores range from 0 to 5, with lower scores indicating greater patient activity:

0. Fully active; able to carry out all usual activities without restrictions

1. Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (e.g., light housework or office work)

2. Ambulatory and capable of self-care, but unable to carry out any activities; up and about more than 50% of waking hours

3. Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

4. Completely disabled; unable to carry out any self-care and totally confined to bed or chair

5. Dead

Any significant changes from baseline or screening will be reported as AE.

3.5.12 Deaths

All deaths will be collected until the end of the study.

3.5.13 Pregnancy

All pregnancies and outcomes of pregnancy should be reported except where the pregnancy is discovered before the study patient has received any study treatment.

3.5.14 General considerations for safety assessments

3.5.14.1 Definition of baseline

Baseline will be defined as the last non-missing measurement of the variable under consideration prior to the intake of the first dose of study treatment (capivasertib, placebo or fulvestrant). That is, the latest result prior to the start of study treatment. If two visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to the first dose with no washout or other intervention in the screening period), the average will be used as the baseline value. For non-numeric laboratory tests (i.e., some of the urinalysis parameters) where taking the average is not possible, the best value would be taken as baseline as this is most conservative. In the scenario where there are two assessments recorded on the same day, one with time recorded and the other without time recorded, the one with the time recorded would be selected as baseline. Where safety data are summarised over time, time on study will be calculated in relation to date of first study treatment.

3.5.14.2 Time windows for safety data

Time windows will be defined for all presentations of safety data that summarise values by visit according to the following conventions:

- The time windows should be exhaustive so that data recorded at any time point (scheduled or unscheduled) has the potential to be summarised. Inclusion within the time window should be based on the actual date and not the intended date of the visit.
- Post dose assessments taken on Cycle 1 Day 1 will be mapped to Cycle 1 Week 1 Day 1.
- For safety data such as vital signs where assessments are scheduled pre-dose and 1-2h post dose, the closest assessment recorded on the same day prior to the start of infusion or post dose closest to 1-hour post dose will be used respectively. If no

measurement is available pre or post on the same day, then that assessment will be missing.

For other safety data scheduled only once per day, the window for visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first post baseline visit will be Day 2). If an even number of days exist between two consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day. Windowing will be derived as long as data permits.

Treatment discontinuation visit will be mapped to the nominal visit including PRO data.

Table 12 Visit window for safety data

Laboratory measurements such as Haematology, Clinical chemistry, Urinalysis, Glucose (fasting), Vital signs, ECOG will use the following visit window.

Window Period	Minimum Day	Target Day	Maximum Day
Cycle 1, Week 3, Day 1 *	2	15	21
Cycle 2, Week 1, Day 1	22	29	35
Cycle 2, Week 3, Day 1 **	36	43	49
Cycle 3, Week 1, Day 1	50	57	70
Cycle 4, Week 1, Day 1	71	85	98
Cycle 5, Week 1, Day 1	99	113	126
Cycle 6, Week 1, Day 1	127	141	154
Cycle 7, Week 1, Day 1	155	169	182
Cycle 8, Week 1, Day 1	183	197	210
Continue every 28 days			
Cycle 16, Week 1 Day 1	211	225	238

* Not applicable for weight; ** Not applicable for glucose (fasting) and weight.

Table 13 Visit window for safety data (with 4 weeks between scheduled assessments)

EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D-5L, PGIS, PGIC

Window Period	Minimum Day	Target Day	Maximum Day

Cycle 2, Week 1, Day 1	2	29	43
Cycle 3, Week 1, Day 1	44	57	70
Cycle 4, Week 1, Day 1	71	85	98
Cycle 5, Week 1, Day 1	99	113	126
Cycle 6, Week 1, Day 1	127	141	154
Cycle 7, Week 1, Day 1	155	169	182
Cycle 8, Week 1, Day 1	183	197	210

Table 14 Visit window for safety data (with 2 weeks between scheduled assessments up to and including Week 12 and then every 4 weeks)

PGI-TT, PRO-CTCAE

Window Period	Minimum Day	Target Day	Maximum Day
Cycle 1, Week 3, Day 1	2	15	21
Cycle 2, Week 1, Day 1	22	29	35
Cycle 2, Week 3, Day 1	36	43	49
Cycle 3, Week 1, Day 1	50	57	63
Cycle 3, Week 3, Day 1	64	71	77
Cycle 4, Week 1, Day 1	78	85	98
Cycle 5, Week 1, Day 1	99	113	126
Cycle 6, Week 1, Day 1	127	141	154
Cycle 7, Week 1, Day 1	155	169	182
Cycle 8, Week 1, Day 1	183	197	210

Table 15 Visit window for safety data (with 12 weeks between scheduled assessments from Cycle 1 onwards)

Laboratory measurements such as Glycosylated haemoglobin (fasting), Lipids (fasting), ECHO (LVEF) will use the following visit window. LVEF results will be summarised for patients from VHP countries only where the data collection is scheduled every 12 weeks.

Window Period	Minimum Day	Target Day	Maximum Day
Cycle 4, Week 1, Day 1	2	85	127
Cycle 7, Week 1, Day 1	128	169	211
Cycle 10, Week 1, Day 1	212	253	295

Table 16 Visit window for safety data (with 12 weeks between scheduled assessments from Cycle 2 onwards)

12-lead ECG

Window Period	Minimum Day	Target Day	Maximum Day
Cycle 2, Week 1, Day 1	2	29	70
Cycle 5, Week 1, Day 1	71	113	154
Cycle 8, Week 1, Day 1	155	197	238

Note, due to the differing assessment schedules, the visit windows may be different for the different endpoints.

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).
- Listings will display all values contributing to a time point for a patient.
- For visit-based summaries, if there is more than one value per patient within a time window then the closest value to the scheduled visit date will be summarised. If the values are equidistant from the nominal visit date, then the earlier value will be used. Data listings will highlight the values used in the summary table, wherever feasible. Note: In summaries of extreme values, all post-baseline values collected are used including those collected at unscheduled visits regardless of which value is closest to the scheduled visit date.
- For summaries at patient level, all values will be included when deriving a patient level statistic such as a maximum regardless of whether they appear in the corresponding visit-based summary.

3.5.14.3 Handling of missing data

Missing safety data will generally not be imputed. However, safety assessments of the form of "< x" (i.e., below the lower limit of quantification) or "> x" (i.e., above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but will be displayed as "< x" or "> x" in the listings.

For missing start dates for AEs and concomitant medications/procedures, the following will be applied:

- Missing day: Impute the 1st of the month unless month is the same as month of the first dose of study drug then impute first dose date.
- Missing day and month: Impute 1st January unless year is the same as first dose date then impute first dose date.
- Completely missing date: Impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

When imputing a start date, ensure that the new imputed date is sensible e.g., prior to the end date of the AE.

For missing stop dates of AEs or concomitant medications/procedures, the following will be applied:

- Missing day: Impute the last day of the month unless month is the same as month of last dose of study drug then impute last dose date.
- Missing day and month: Impute 31st December unless year is the same as last dose date then impute last dose date.
- Completely missing: Look at whether the AE/medication is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is missing, then assume that AE is still present / medication is still being taken (i.e. do not impute a date). If the AE/medication has stopped and start date is prior to first dose date then impute the 1st dose date, if it started on or after first dose date then use the last dose date, last visit date or date of death, whichever is latest, as the imputed date.

Flags will be retained in the database indicating where any programmatic imputation has been applied, and in such cases, any durations would not be calculated.

If a patient is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided:

- Missing day only: Using the 1st of the month.
- Missing day and month: Using the 1st January.

If there is evidence of death but the date is entirely missing, it will be treated as missing, i.e., censored at the last known alive date.

3.6 Pharmacokinetic (PK) variables

PK concentration data will be collected as described in Section 8.5 of the CSP.

Capivasertib plasma concentration variables, C_{trough} (pre-dose), C_{1h}, C_{4h} (post-dose) will be analysed in the overall population. $AUC_{0\text{-}12h}$, C_{max} and t_{max} will be derived using a non-compartmental analysis in a subpopulation of approximately 6 Japanese patients with rich PK sampling. In addition, population PK model parameters, including variability parameters, will be estimated as data permits.

3.7 Biomarkers

Mandatory collection of tumour tissue and blood samples for biomarker research is required as part of this study. Optional tumour tissue samples should be collected from consenting patients only. A detailed description of samples that will be collected from all patients in this study are specified in Sections 8.7.1 and 8.7.2 of the CSP.

3.8 Other variables

3.8.1 Prior and concomitant medications and therapies

All therapies (drug and non-drug), including herbal preparations, whether prescribed or over-the-counter, that are used within the four weeks prior to initiation of study treatment up until 30 days (+ 7-day window) following last dose of study treatment will be recorded on the eCRF. Details include generic and/or brand names of the medications, World Health Organisation Drug Dictionary (WHO-DD) encoding (using the latest or current WHO-DD version), reason for use, route, dose, dosing frequency, and start and stop times.

Medications received prior to, concomitantly, or post-treatment will be coded using the AstraZeneca Drug Dictionary Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications are those taken prior to study treatment with a stop date prior to the first dose of study treatment (capivasertib, placebo or fulvestrant).

Concomitant medications are those with a stop date on or after the first dose date of study treatment (capivasertib, placebo or fulvestrant) and could have started prior to or during treatment.

Post-treatment medications are those with a start date after the last dose date of study treatment (capivasertib, placebo or fulvestrant).

Missing start and stop dates for medications will be handled using the rules in Section 3.5.14.3. Missing coding terms should be listed and summarised as "Not coded".

4 ANALYSIS METHODS

The primary objective of this study is to assess the efficacy of capivasertib + fulvestrant (Arm A) compared to placebo + fulvestrant (Arm B) in terms of PFS (in the overall and the *PIK3CA/AKT1/PTEN*-altered populations) in patients with locally advanced (inoperable) or metastatic hormone receptor positive (HR+/HER2−) breast cancer following recurrence or progression on or after third generation AI therapy.

Results of all statistical analysis will be presented using a 95% confidence interval (CI, 2-sided), and 2-sided p-value, unless otherwise stated.

The intention of the study is to demonstrate the superiority of capivasertib + fulvestrant over placebo + fulvestrant in either or both of the overall and *PIK3CA/AKT1/PTEN*-altered populations

The formal statistical analysis will be performed to test the following main hypotheses:

- Null hypothesis: No difference between Arm A and Arm B
- Alternative hypothesis: Difference between Arm A and Arm B

4.1 General principles

Efficacy and PRO data will be summarised and analysed on the FAS and altered subgroup FAS. Safety and treatment exposure data will be summarised based upon the Safety Analysis Set and on the Altered Subgroup Safety Analysis Set for the *PIK3CA/AKT1/PTEN*-altered subgroup. Study population and demography data will be summarised based upon the FAS. PK data will be analysed using the PK analysis set and Japanese PK data will be analysed using the Japan PK analysis set.

The below mentioned general principles will be followed throughout the study:

- All analyses and reporting will be by treatment arm.
- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, upper and lower quartiles, minimum, and maximum. For log-transformed data it is more appropriate to present geometric mean, coefficient of variation (CV), median, minimum and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.

- Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment group. Overall totals will be calculated for baseline summaries only.
- For continuous data, the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data. Summary statistics will be presented only when number of observations is at least a minimum of 20 and >1/3 of patients dosed at a time point within at least one treatment group, unless otherwise stated.
- For categorical data, percentages will be rounded to 1 decimal place.
- SAS® version 9.4 (or higher) will be used for all analysis.

In general, for efficacy and PRO endpoints the last observed measurement prior to randomisation will be considered the baseline measurement. However, if an evaluable assessment is only available after randomisation but before the first dose of randomised treatment then this assessment will be used as baseline. For safety endpoints the last observation before the first dose of study treatment (capivasertib, placebo or fulvestrant) will be considered the baseline measurement unless otherwise specified. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose.

For safety endpoints, day 1 will be treatment start day and for efficacy endpoints day 1 will be randomisation day.

Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose.

In all summaries change from baseline variables will be calculated as the post-treatment value minus the value at baseline. The percentage change from baseline, where reported, will be calculated as (post-baseline value - baseline value) / baseline value x 100.

4.1.1 Data cut-offs

The analyses will be performed at the following data-cut offs (DCO).

	Analysis	**#Events (Maturity of data)**	
		Overall population	**Altered population**
DCO1	PFS Primary	542 (77%)	217 (77%)

DCO2	OS Interim	394 (56%)	158 (56%)
DCO3	OS Final	492 (70%)	197 (70%)

After the PFS primary analysis, if PFS in the overall population and in altered subgroup FAS is not significant, no further analysis will be done.

4.2 Analysis methods

Table 17 details which endpoints are to be subject to formal analysis, together with pre-planned sensitivity analyses, making it clear which is regarded as primary for the endpoint.

Table 17 Statistical analyses to be conducted and pre-planned sensitivity analyses

Endpoints analysed	Notes
Progression Free Survival	Primary objective Stratified log-rank test providing a p-value and stratified Cox proportional hazard model providing hazard ratio (HR) (95% CI and alpha adjusted CI) for formal primary analysis using RECIST v1.1 based on Investigator assessments for FAS and for the *PIK3CA/AKT1/PTEN*-altered subgroup. Kaplan-Meier plots will be presented by treatment group for the overall and for the *PIK3CA/AKT1/PTEN*-altered subgroup. Sensitivity and supplementary analysis Stratified log-rank test for the FAS using investigator assessment to assess evaluation-time bias. Stratified log-rank test for the FAS using investigator assessment and KM plot of time to censoring where censoring indicator of the primary analysis is reversed for the evaluation of attrition bias. Stratified log-rank test for the FAS using BICR assessments for the evaluation of ascertainment bias. Stratified log-rank test for the FAS using investigator assessments for the evaluation of deviation bias if applicable. Stratified log-rank test providing a p-value and stratified Cox proportional hazard model providing hazard ratio (HR) (95% CI) using RECIST v1.1 based on Investigator assessments for FAS with censored PFS events due to COVID-19 infection related deaths. Subgroup analysis using Cox proportional hazard model based on investigator assessment with KM plots

Endpoints analysed	Notes
	for selected subgroups for FAS and for the *PIK3CA/AKT1/PTEN*-altered subgroup. CCI [redacted]
Overall Survival	<u>Secondary objective</u> Stratified log-rank test providing a p-value and stratified Cox proportional hazard model providing HR (95% CI and alpha adjusted CI) for formal analysis for FAS and for the *PIK3CA/AKT1/PTEN*-altered subgroup. Kaplan-Meier plots will be presented by treatment group. <u>Sensitivity and supplementary analysis</u> KM plot of time to censoring where censoring indicator of the primary analysis is reversed – evaluation of attrition bias. Stratified log-rank test providing a p-value and stratified Cox proportional hazard model providing HR (95% CI) for FAS with censored COVID-19 related deaths. Subgroup analysis using Cox proportional hazard model for FAS and for the *PIK3CA/AKT1/PTEN*-altered subgroup.
Progression Free Survival 2	Stratified log-rank test using investigator assessment for FAS and the *PIK3CA/AKT1/PTEN*-altered subgroup.
Objective Response Rate	Logistic regression adjusted for stratification factors according to RECIST v1.1 based on Investigator assessments for FAS and for the *PIK3CA/AKT1/PTEN*-altered subgroup.
Duration of Response	KM plot of DoR according to RECIST v1.1 based on Investigator assessments for responders for FAS and for the *PIK3CA/AKT1/PTEN*-altered subgroup.
Clinical Benefit Rate	Logistic regression adjusted for stratification factors according to RECIST v1.1 based on Investigator assessments for FAS and for the *PIK3CA/AKT1/PTEN*-altered subgroup.
Time to First Subsequent Chemotherapy or death (TFSC).	Stratified log-rank test providing a p-value and stratified Cox proportional hazard model providing hazard ratio (HR) (95% CI) for FAS and for the *PIK3CA/AKT1/PTEN*-altered subgroup

Endpoints analysed	Notes
Time to definitive deterioration of the ECOG performance status	Stratified log-rank test providing a p-value and stratified Cox proportional hazard model providing hazard ratio (HR) (95% CI) for FAS and for the *PIK3CA/AKT1/PTEN*-altered subgroup.
Change from baseline in each scale/item of EORTC QLQ-C30, and EORTC QLQ-BR23	Summary and descriptive statistics for FAS and for the *PIK3CA/AKT1/PTEN*-altered subgroup.
Change from baseline in key symptoms, functions, global health status/QoL of EORTC QLQ-C30 and QLQ-BR23	MMRM analysis for randomised patients with an evaluable baseline assessment and at least one evaluable post baseline assessment for FAS and for the *PIK3CA/AKT1/PTEN*-altered subgroup.
Time to physical function, fatigue, pain and appetite loss and global health status/QoL deterioration using EORTC QLQ-C30	Stratified log-rank test (for p-value), HR from stratified Cox model providing HR (95% CI), KM plot for FAS and for the *PIK3CA/AKT1/PTEN*-altered subgroup.
Improvement rates for key PRO endpoints (EORTC QLQ-C30)	Logistic regression with odds ratio, 95% CI and p-value for FAS and for the *PIK3CA/AKT1/PTEN*-altered subgroup
Patient global and treatment- related symptoms (PGI-TT and PRO-CTCAE)	Summary and descriptive statistics for Safety and Altered Safety Analysis Set
EQ-5D-5L (health state utility values and visual analogue scale)	Summary statistics for health state utilities, including change from baseline for FAS and for the *PIK3CA/AKT1/PTEN*-altered subgroup.
Healthcare resource use	Descriptive statistics (as appropriate, including means, median, ranges or frequencies and percentages) for FAS and the *PIK3CA/AKT1/PTEN*-altered subgroup.
Plasma concentration and PK parameters	Descriptive statistics of capivasertib plasma concentrations pre-dose (C_{trough}) and post-dose (C_{1h} and C_{4h}) and population PK modelling, as data permits for PK and Japan Intensive Pharmacokinetic Analysis Set.

Endpoints analysed	Notes
	AUC $_{0\text{-}12h}$, C_{max} and t_{max} in a subpopulation of approximately 6 Japanese patients for Japan Intensive Pharmacokinetic Analysis Set.
Safety and tolerability	Summary and descriptive statistics for adverse events, laboratory findings, vital signs, ECG and physical examination for Safety and Altered Safety Analysis Set

AKT1 Alpha serine/threonine-protein kinase 1; DoR Duration of response; EORTC European Organisation for Research and Treatment of Cancer; EQ-5D-5L European Quality of Life 5-Domain 5-Level Scale; HR Hazard ratio; HRQoL Health related quality of life; KM Kaplan Meier; MMRM Mixed-effect model repeated measure; OS Overall survival; PFS Progression free survival; PGIC Patient Global Impression-Change; PGIS Patient Global Impression-Severity; PGI-TT Patient Global Impression-Treatment Tolerability; PIK3CA phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PK pharmacokinetics; PRO Patient reported outcomes; PRO-CTCAE Patient reported outcomes Common Terminology Criteria for Adverse Events; PTEN phosphatase and tensin homolog; EORTC QLQ-BR23 EORTC Quality of Life Questionnaire breast cancer specific module; QLQ-C30 30-Item Core Quality of Life Questionnaire; QoL Quality of life; RECIST Response Evaluation Criteria in Solid Tumours.

4.2.1 Multiplicity

To control the family-wise error rate in the strong sense at 5% for the treatment comparisons in OS and PFS, a predefined MTP with an alpha-exhaustive recycling strategy (Burman et al 2009) taking into account intrinsic correlation between test statistics (Spiessens and Debois 2010), will be applied. The MTP is outlined in Figure 3. According to alpha (test mass) splitting and alpha recycling, if the higher-level hypothesis in the MTP is rejected for superiority, then the next lower level hypothesis will be tested. The test mass that becomes available after each rejected hypothesis is recycled to lower level hypotheses not yet rejected.

Tests will be grouped into 2 main families: one for the comparisons in PFS, the other for the comparisons in OS. Within the PFS and OS families, there are 2 sets of tests, one in the overall population, the other in the altered subgroup. The PFS family will be tested first, the OS family will be tested later (Figure 3). This testing procedure stops when the entire test mass is allocated to non-rejected hypotheses. Implementation of this predefined testing procedure, including recycling, will control the family wise type I error in the strong sense at 5% (2-sided), among all key hypotheses.

If the OS endpoint is successful at either interim or final analysis in both the overall population and *PIK3CA/AKT1/PTEN*-altered subgroup, the remaining alpha will be recycled to test ORR in the *PIK3CA/AKT1/PTEN*-altered subgroup. If significant, the remaining alpha will be recycled to test ORR in the overall population. Data at PFS primary analysis DCO will be used to test ORR.

The PFS Primary Analysis will take place after PFS reaches approximately 77% maturity (542 events) in the overall population and approximately 77% maturity in patients whose tumours

harbour an eligible *PIK3CA/AKT1/PTEN* alteration, based on a prevalence of ~40-45% (and 174 events will have been observed if a test failure rate is 20%).

Table 18 Statistical consideration for PFS endpoint

Analysis	Significance level	Number of events (assuming 20% test failure rate)	Critical value in HR [corresponding median PFS [a]]	Power (Assuming HR=0.64)
PFS Final Analysis (altered subgroup, assuming 77% maturity)	0.021[b]	217 (174)	0.73 (7.5 months) [0.71 (7.7 months)]	83.7% (73.9%)
	0.05[c]	217 (174)	0.77 (7.2 months) [0.74 (7.4 months)]	90.8% (83.7%)
PFS Final Analysis (overall population, assuming 77% maturity)	0.035	542	0.83 (6.6 months)	> 99%

HR, hazard ratio; PFS, progression-free survival.

[a] Assuming median PFS for placebo + fulvestrant arm is 5.5 months and PFS is exponentially distributed.

[b] Assuming the null hypothesis for the PFS primary analysis in the overall population is not rejected at α=0.035 level and the observed ratio of the number of events between the altered subgroup and overall population is 0.4.

[c] Assuming the null hypothesis for the PFS primary analysis in the overall subgroup is rejected at α=0.035 level.

After both the pre-defined PFS endpoints have been tested, the remaining alpha will be used for testing OS in the *PIK3CA/AKT1/PTEN*-altered population and subsequently for OS in the overall population at the OS Interim Analysis. ORR in the *PIK3CA/AKT1/PTEN*-altered population and the overall population will be tested sequentially only if OS in the overall population and *PIK3CA/AKT1/PTEN*-altered population is statistically significant.

The OS Interim Analysis is expected to occur when approximately 394 OS events have been observed in the overall population (56% maturity, 80% information fraction). If the time between the PFS primary analysis and the OS interim analysis is approximately 3 months or less, then the PFS DCO may be delayed and the analyses combined. The OS Final Analysis will take place when approximately 70% maturity has been observed in both the overall and the *PIK3CA/AKT1/PTEN*-altered populations. The exact significance level will be determined

according to the O'Brien & Fleming method (Lan and DeMets 1983) based on the actual number of events observed at the OS Interim Analysis.

Following FDA advice, a small alpha spend will be applied to the analysis of no OS detriment assessed at the time of the PFS primary analysis. This will use a bespoke alpha spending function with 0.0001 alpha assigned to DCO1 in each of the overall and *PIK3CA/AKT1/PTEN*-altered populations. The remaining OS analyses will use the planned cumulative alpha at DCO2 and DCO3 from the 2-look O'Brien & Fleming method.

Table 19 Statistical consideration for OS endpoint

Analysis	**Significance level**	**Number of events**	**Critical value in HR (critical value in median OS [a])**	**Power (Assuming HR=0.74)**
OS Interim Analysis (altered subgroup, assuming 80% information fraction)	0.0056[b]	158 (127)	0.642 (33.7 months) [0.610 (40.9 months)]	13% (6%)
	0.0244[c,d]	158 (127)	0.698 (30.8 months) [0.670 (35.2 months)]	28% (16%)
OS Final Analysis (altered population)	0.0133[b]	197 (158)	0.702 (29.3 months) [0.673 (32.0 months)]	36% (21%)
	0.0429[c,d]	197 (158)	0.749 (27.9 months) [0.724 (29.7 months)]	53% (36%)
OS Interim Analysis (overall population, assuming 80% information fraction)	0.0056[b]	394	0.756 (28.5 months)	44%
	0.0244[c,d]	394	0.769 (27.2 months)	64%
OS Final Analysis (overall population)	0.0133[b]	492	0.799 (26.5 months)	80%
	0.0429[c,d]	492	0.833 (25.8 months)	90%

HR, hazard ratio; OS, overall survival.

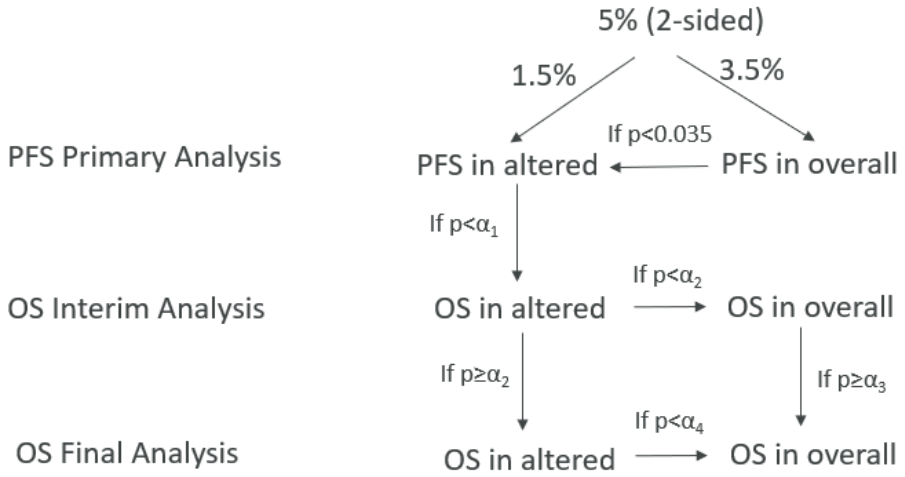
[a] Assuming median OS for placebo + fulvestrant arm is 23 months and OS follows a Weibull distribution with β=1.5.

[b] Assuming the null hypothesis for the PFS primary analysis in the overall population is not rejected at α = 0.035 level.

[c] Assuming the null hypothesis for PFS primary analysis in the overall population is rejected at α = 0.035 level.

[d] With an OS alpha spend of 0.0001 at the PFS primary analysis in each of the altered and overall populations, assuming 80% information fraction is observed for both of the altered and overall population, the significance levels to be used for OS at DCO1, DCO2 and DCO3 analyses are 0.0001, 0.0244, and 0.0429 respectively for both populations.

Figure 3 Illustration of data cut-offs and associated treatment comparisons



The significance level of α_1 at PFS primary analysis in the altered subgroup will be determined as follows:

- If the p-value for PFS in the overall population is significant at 3.5% level, then the α level of 0.035 tested for the overall population will be recycled, making α_1=0.05.
- If the p-value for PFS in the overall population is not significant at 3.5% level, then the α_1 is determined by the observed ratio of #events in the altered subgroup and overall population using Spiessens and Debois method.

The cumulative significance level at OS interim analysis and at OS final analysis for the altered subgroup will be determined by the observed information fraction (O'Brien & Fleming approach [Lan and DeMets 1983]) based on the remaining α available:

- If the p-value for PFS in the overall population is significant at 3.5% level, then the remaining α=0.05
- If the p-value for PFS in the overall population is not significant at 3.5% level, then the remaining α=0.015.

The actual significance level of α_2 at OS interim analysis and α_4 at OS final analysis for the altered subgroup will be determined by the cumulative α spend at OS interim and final analysis, while allowing for an OS α spend of 0.0001 at PFS primary analysis for the altered subgroup

Similarly, if the p-value for OS in the altered subgroup is significant at α_2 level at the OS interim analysis, OS in the overall population will be tested at α_3 level, which is determined by the cumulative α spend at OS interim and final analysis for the overall population using the O'Brien & Fleming approach [Lan and DeMets 1983] based on the remaining α available, while allowing for an OS α spend of 0.0001 at PFS primary analysis for the overall population. If the p-value for OS in the altered subgroup is significant at α_4 level at the OS final analysis, the remaining α available to test OS in the overall population at OS final analysis will be used.

4.2.2 Pooling strategy

For all endpoints, a pooling strategy will be applied if the number of responses / events in the individual stratum are too small for a meaningful analysis (i.e. less than 10 responses/events in any stratum across both treatments or less than 2 responses/events in any treatment arm within any stratum; a stratum is defined as strata1*strata2*…strataX; so, with 3 stratification factors each with 2 levels, we have 2*2*2=8 stratum). If there are primary or secondary endpoints that still do not conform to this criterion, the randomisation stratification factors will be dropped in the following order by their importance: geographic location, liver metastases, CDK 4/6 inhibitor. This will be done for each individual endpoint to be analysed and consequently the strata used in the analysis may vary by endpoint. All the sensitivities for each endpoint, will use the same strata as the primary model within each population, for that endpoint, unless there are < 10 responses/events in any stratum or < 2 responses/events in any treatment arm within any stratum, and then an unadjusted model will be used. If required, unadjusted sensitivity analyses of each of the endpoints may also be performed.

4.2.3 Dual primary efficacy endpoint

4.2.3.1 PFS in the overall population

The primary endpoint PFS in the overall population based on the investigator RECIST v1.1 will be analysed using a log-rank test stratified by geographic region (Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia), liver metastases (yes vs no), and prior use of CDK4/6 inhibitors (yes vs no) for generation of the p-value and using a method that corresponds to the Breslow approach for handling ties (Breslow N, 1974). To estimate the effect of treatment, the HR together with its 95% CI and CI adjusted for multiplicity will be estimated from a stratified Cox proportional hazards model (Cox DR, 1972) with ties = Efron and the stratification variables included in the strata statement and the CI calculated using the profile likelihood approach. A HR less than 1 will favour capivasertib + fulvestrant.

The stratification variables in the statistical modelling will be based on the values entered into the interactive web response system (IWRS) at randomisation, even if it is subsequently discovered that these values were incorrect. A sensitivity analysis may be carried out using the (correct) stratification variables data collected in the eCRF.

Kaplan-Meier plots of PFS will be presented by treatment group. Summaries of the number and percentage of patients experiencing a PFS event and the type of event (RECIST v1.1 progression or death) over time at 6, 9 and 12 months will be provided along with the median PFS for each treatment group. In addition, the number and percentage of patients censored in the analysis as well as by reason for censoring will be provided for each treatment group.

The treatment status at progression of patients at the time of analysis will be summarised. This will include the number (%) of patients who were on treatment at the time of progression, the

number (%) of patients who discontinued study treatment prior to progression, the number (%) of patients who have not progressed and were on treatment or discontinued treatment. This will also provide distribution of number of days prior to progression for the patients who have discontinued treatment.

Assumptions of proportionality

The assumption of proportionality will be assessed. Proportional hazards will be tested firstly by examining plots of complementary log-log (probability of PFS) versus log (time) and, if these raise concerns, by fitting a time dependent covariate (adding a treatment-by-time or treatment-by-ln(time) interaction term) to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect can be described by presenting piecewise HR calculated over distinct time-periods for example 0 – 6 m, 6 – 12 m etc. In such circumstances, the HR from the primary analysis can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves.

Sensitivity and supplemental analysis

The following sensitivity and supplemental analysis will also be performed:

Evaluation-time bias

Sensitivity analyses in the overall population will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST v1.1 assessment will be analysed using a stratified log-rank test. For patients, whose death was treated as PFS event, the date of death will be used to derive the PFS time used in the analysis. This approach has been shown to be robust even in highly asymmetric assessment schedules (Sun and Chen 2010).

Attrition bias

Attrition bias in the overall population will be assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following 2 or more missed assessments will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. This analysis will be supported by a Kaplan-Meier plot of the time to censoring where the censoring indicator of the PFS analysis is reversed.

Ascertainment bias

Ascertainment bias in the overall population will be assessed by analysing the BICR data. The stratified log rank test will be repeated on PFS using the BICR data based upon RECIST v1.1. The HR and CI will be presented.
If there is an important discrepancy between the primary analysis using the site investigator data and this sensitivity analysis using BICR data, then the proportion of patients with site but no central confirmation of progression will be summarised; such patients have the potential to induce bias in the central review due to informative censoring. An approach of imputing an event at the next visit in the central review analysis may help inform the most likely HR value (Fleischer et al 2011), but only if an important discrepancy exists.
Disagreements between investigator and central reviews of RECIST v1.1 progression will be presented for each treatment group.

Deviation bias (if meaningful to do)

As a sensitivity analysis to the primary endpoint of PFS, an analysis excluding patients with deviations that may affect the efficacy of the trial therapy will be performed if > 10% of patients did not have the intended disease or indication or did not receive any randomised therapy. A stratified log-rank test will be repeated using the investigator RECIST v1.1 data, using the same ties and stratification factor as described for the primary analysis of PFS. The HR and 95% CI will be presented.

COVID-19 impact

A sensitivity analysis will be conducted to assess for the potential impact of COVID deaths on PFS. This will be assessed by repeating the PFS analysis except that any patient who had a PFS event due to death where primary/secondary cause of death was due to COVID-19 Infection, or a COVID-19 infection reported as a fatal AE, will be censored at their last evaluable assessment prior to their COVID infection death date.

Additional supportive analyses

In addition, the number of patients prematurely censored will be summarised by treatment arm together with baseline prognostic factors of the prematurely censored patients. A patient would be defined as prematurely censored if they had not progressed (or died in the absence of progression) and the latest scan prior to DCO was more than one scheduled tumour assessment interval plus 2 weeks prior to the DCO date.

Additionally, summary statistics will be given for the number of days from censoring to DCO for all censored patients.

A summary of the duration of follow-up will be summarised using median time from randomisation to date of censoring (date last known to have not progressed) in censored (not progressed) patients only, presented by treatment group.

Additionally, summary statistics for the number of weeks between the time of progression and the last evaluable RECIST v1.1 assessment prior to progression will be presented for each treatment group.

Summaries of the number and percentage of patients who miss two or more consecutive RECIST assessments will be presented for each treatment group.

All of the collected RECIST v1.1 data will be listed for all randomised patients.

In addition, a summary of new lesions (i.e. sites of new lesions) will be produced.

Subgroup analyses

Subgroup analyses will be conducted comparing PFS between capivasertib + fulvestrant versus placebo + fulvestrant in the following plausible and CCI [redacted]

Plausible Subgroups

- *PIK3CA/AKT1/PTEN* mutation status in tissue (*PIK3CA/AKT1/PTEN*-altered vs *PIK3CA/AKT1/PTEN* non-altered)
- Prior chemotherapy in the locally advanced (inoperable) or metastatic disease (Y/N)

CCI [redacted]

For these subgroup analyses any patient with missing values will be excluded from that particular subgroup unless unknown category included.

In addition, Kaplan Meier plot will be provided for the *PIK3CA/AKT1/PTEN* non-altered subgroup including patients with unknown biomarker results and for subgroups by prior CDK 4/6 inhibitors use. The plot will include HR together with its corresponding 95% CI from the Cox proportional hazard model stratified by the randomisation stratification variables.

Other baseline variables may also be assessed if there is clinical justification or an imbalance is observed between the treatment arms. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors.

For each subgroup level of a factor, the HR and 95% CI will be calculated from a Cox proportional hazards model that only contains term for treatment. The Cox models will be fitted using SAS® PROC PHREG with the Efron method to control for ties and using a BY statement for the subgroup factor. These HRs and associated 2-sided 95% profile likelihood CIs will be summarised and presented on a forest plot, along with the results of the overall primary analysis. No adjustment to the significance level for testing of the subgroup will be made, since all these analyses will be considered supportive of the primary analysis of PFS. Additional sensitivity analyses using the same methodology as described for the primary PFS endpoint in Section 4.2.3.1 may also be considered.

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events across both treatment groups within a subgroup), the HR and CI will not be produced for that subgroup. In this case, only descriptive summaries will be provided.

4.2.3.2 PFS in the *PIK3CA/AKT1/PTEN*-altered subgroup

PFS in the *PIK3CA/AKT1/PTEN*-altered subgroup will be analysed as described for the PFS in the overall population. For the analysis in the *PIK3CA/AKT1/PTEN*-altered subgroup, the Cox proportional hazard model stratified by the randomisation stratification variables will be fitted. The effect of treatment will be estimated by the HR together with its corresponding 95% CI and CI adjusted for multiplicity. Kaplan Meier plots will be presented by treatment group. All sensitivity analyses outlined for PFS in Section 4.2.3 will be repeated in the *PIK3CA/AKT1/PTEN*-altered subgroup.

Subgroup analysis will be repeated in the *PIK3CA/AKT1/PTEN*-altered subgroup.

4.2.4 Secondary efficacy endpoints

4.2.4.1 OS in the overall population

The secondary endpoint OS will be analysed using a stratified log-rank test using similar methodology as described for primary PFS endpoint in Section 4.2.3.

The effect of treatment will be estimated by the hazard ratio (HR) together with its corresponding 95% CI, CI adjusted for multiplicity and p-value for the FAS. For the analysis in the overall population, the model will be stratified by randomisation stratification variables.

Kaplan-Meier (KM) plots of OS will be presented by treatment arm. Summaries of the number and percentage of patients experiencing an OS event over time at 18, 24 and 30 months will be provided along with the median OS for each treatment group.

Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow-up and those who have withdrawn consent will be provided along with the median OS for each treatment.

Assumptions of proportionality

If hazards are found to be non-proportional, additional CCI [redacted]

Sensitivity and supplemental analysis

The following sensitivity and supplemental analysis will be performed.

Attrition bias

A sensitivity analysis for OS in the overall population will examine the censoring patterns to rule out attrition bias with regard to the primary treatment comparisons, achieved by a Kaplan-Meier plot of time to censoring where the censoring indicator of OS is reversed.

The number of patients prematurely censored will be summarised by treatment arm. A patient would be defined as prematurely censored if their survival status was not defined at the DCO.

In addition, duration of follow-up will be summarised using medians:

- In all patients: Time from randomisation to the date of death (i.e. overall survival) or to the date of censoring (date last known to be alive) for censored patients regardless of treatment arm.
- In censored patients who are alive at DCO only: Time from randomisation to date of censoring (date last known to be alive) for each arm.

COVID-19 impact

A sensitivity analysis will be conducted to assess for the potential impact of COVID-19 deaths on OS in the overall population. This will be assessed by repeating the OS analysis except that any patient who had a death with primary/secondary cause as COVID-19 infection, or a COVID-19 infection reported as a fatal AE will be censored at their COVID infection death date.

Subgroup analysis

Subgroup analyses will be conducted comparing OS between capivasertib + fulvestrant versus placebo + fulvestrant in the overall population as described for PFS endpoint in Section 4.2.3 for the overall population.

4.2.4.2 OS in the *PIK3CA/AKT1/PTEN*-altered subgroup

The secondary endpoint OS in the *PIK3CA/AKT1/PTEN*-altered subgroup will be analysed using a stratified log-rank test using similar methodology as described for primary PFS endpoint in Section 4.2.3.

Subgroup analyses will be performed in the *PIK3CA/AKT1/PTEN*-altered subgroup.

4.2.4.3 Progression Free Survival 2 (PFS2) in the overall and altered FAS populations

PFS2 in the overall FAS and *PIK3CA/AKT1/PTEN*-altered populations will be analysed using a stratified log rank test, using the same methodology as described for the primary PFS endpoint for the overall population. The PFS2 analysis in the overall population will be stratified by the stratification factors. The effect of treatment will be estimated by the HR together with its corresponding 95% CI. Kaplan Meier plots will be presented by treatment group.

The sensitivity analysis outlined for PFS in Section 4.2.3 will not be repeated for PFS2 with the exception of a KM plot of the time to censoring where the censoring indicator of the PFS2

event is reversed (what was originally a censored event in the analysis becomes an actual event and what originally was a PFS2 event becomes a censored event).

The number and percentage of patients experiencing a PFS2 event and the type of progression will also be summarised by treatment arm. Time from randomisation to second progression will be summarised by treatment arm.

4.2.4.4 Objective Response Rate (ORR) in the overall and altered FAS populations

The ORR will be based on the site investigator RECIST v1.1 data and using all scans regardless of whether they were scheduled or not. Subjects who discontinue randomized treatment without progression, receive a subsequent anticancer therapy (note that for this analysis radiotherapy is not considered a subsequent anticancer therapy) and then respond will not be included as responders in the ORR.

ORR will be analysed for both the overall population and the *PIK3CA/AKT1/PTEN*-altered subgroup. The ORR will be compared between capivasertib + fulvestrant vs placebo + fulvestrant using logistic regression models adjusting for the stratification factors. The results of the analysis will be presented in terms of an odds ratio (an odds ratio greater than 1 will favour capivasertib + fulvestrant) together with its associated profile likelihood 95% CI (e.g. using the option 'LRCI' in SAS procedure GENMOD) and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model). This analysis will be performed in a subset of the FAS including all patients with measurable disease at baseline.

If there are not enough responses for a meaningful analysis (it is not considered appropriate to present analyses where there are less than 20 responders across both treatment groups within a subgroup) using logistic regression, then a Cochran-Mantel Haenszel (CMH) test will be presented. The CMH test will be stratified using the same stratification factors as the dual primary endpoints. The results of the analysis will be presented in terms of an odds ratio together with the 95% CI and p-value. The odds ratio, 95% CI and p-value will be obtained using SAS PROC FREQ and the CMH test option. The STRATUM variable used in the TABLE statement will be based on the stratification factors. If the number of responders is ≤ 5 for any treatment arm, then a Fisher's exact test using mid p-values will be presented.

Summaries will be produced that present the number and percentage of patients with a tumour response (CR/PR). Overall visit response data will be listed for all patients with measurable disease at baseline.

4.2.4.5 Duration of Response (DoR) in the overall and altered FAS populations

Descriptive data will be provided for the DoR in both populations in patients responding to treatment based on the Investigator assessment of RECIST v1.1, including the associated

Kaplan-Meier curves, for each treatment group and summary of median DoR will be presented. Swimmer plots that clearly show the profile of each patient who responded will also be produced. Only patients who have a response will be included in this analysis.

There will be no formal comparison of treatment groups or associated p-value.

4.2.4.6 Clinical Benefit Rate (CBR) in the overall and altered FAS populations

The CBR in the overall and the *PIK3CA/AKT1/PTEN*-altered populations will be analysed as described for the ORR analysis in Section 4.2.4.4.

4.2.4.7 Time to definitive deterioration of the ECOG performance status in the overall and altered FAS populations

Time to definitive deterioration of the ECOG performance status in the overall and the *PIK3CA/AKT1/PTEN*-altered populations will be analysed as described for the PFS endpoint in Section 4.2.3.

4.2.4.8 Patient reported outcomes (PRO)

All items/questionnaires will be scored according to published scoring guidelines. PRO analyses will be based on the FAS for the overall population and the *PIK3CA/AKT1/PTEN*-altered population, unless otherwise indicated. The PRO-CTCAE and PGI-TT will be based on the Safety and Altered Safety Analysis Set.

Compliance rates summarising questionnaire completion at each visit will be tabulated.

4.2.4.8.1 EORTC QLQ-C30

EORTC QLQ-C30 analyses will be produced for FAS and in *PIK3CA/AKT1/PTEN*-altered population, both populations including patients who have an evaluable baseline assessment and at least one evaluable post-baseline assessment, where appropriate.

Adjusted mean change from baseline

The primary assessment of symptoms, impacts, and HRQoL will focus on comparing mean change from baseline in the global health status/QoL, functions (physical, role, cognitive, social, and emotional), multi-term symptoms (fatigue, pain, nausea/vomiting), and single items (dyspnoea, insomnia, appetite loss, constipation and diarrhoea) score between treatment groups. The analysis population for mean change in HRQoL, functions, or symptoms data will be all patients in FAS with an evaluable baseline assessment and at least 1 evaluable post-baseline assessment. The analysis will compare the average treatment effect from the point of randomisation until the time point with excessive missing data (i.e. exclude the first visit with < 20 observations in either arm, and all subsequent visits). The analysis will be repeated for altered subgroup FAS.

Change from baseline will be derived using a mixed model repeat measures (MMRM) analysis of all the post-baseline scores for each visit. The model will include treatment, visit, treatment-by-visit interaction, and stratification factors liver metastases (yes vs no), prior use of CDK4/6 inhibitors (yes vs no) and geographic region (Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia) as explanatory variables and the baseline score and baseline score by visit as covariates, and patient will be included as a random effect. Adjusted mean change from baseline estimates per treatment group and corresponding 95% CIs will be presented along with an overall estimate of the treatment difference, 95% CI. An unstructured covariance matrix will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom. The following provides sample code for implementing the MMRM analysis:

```
proc mixed data=data;
class usubjid TRT VISIT strat1 strat2 strat3;
model CFBL = trt visit bl TRT*VISIT BL*VISIT strat1 strat2 strat3 / noint solution
ddfm=kr;
repeated VISIT / type=un subject=usubjid r;
*estimate differences between means at each visit;
*estimate LS means at each visit for each treatment;
lsmeans TRT*VISIT / cl;
lsmeans TRT / cl;
run;
```

where TRT is the randomised treatment, VISIT is the visit, strat1, strat2 and strat3 are the stratification factors, CFBL is the change from baseline score, and BL is the baseline score. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: Toeplitz with heterogeneity, autoregressive with heterogeneity, Toeplitz, autoregressive and compound symmetry.

The adjusted Least Square (LS) means estimates along with corresponding 95% confidence intervals will be presented for each treatment group, and the treatment differences. Graphical presentation of adjusted LS means estimates by visit for each treatment group will be produced.

Time to deterioration

Additional analyses of symptoms, functions, and HRQoL will focus on time to deterioration (TTD), which will be analysed for FAS and in *PIK3CA/AKT1/PTEN*-altered population using a stratified log-rank test as described for the PFS and OS endpoints (Section 4.2.3 and Section 4.2.4.1). Separate analyses will be conducted for global health status/QoL, physical function, role function, multi-term symptoms (fatigue and pain), and single item (appetite loss). The effect of capivasertib + fulvestrant vs placebo + fulvestrant will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment group. A forest plot by scale/item will also be produced with the hazard ratio estimates, and the associated 95% CI. Summaries of the number and percentage of patients who have an event as well as who were censored will be provided along with the medians for each treatment.

If there are too few events available for a meaningful analysis of a particular population (it is not considered appropriate to present analyses where there are less than 20 events across both treatment groups within a subgroup), the HR and CI will not be produced for that population. In this case, only descriptive summaries will be provided.

Patients with no evaluable baseline or a baseline score that cannot be deteriorated will be excluded from this analysis.

Response by visit

Summary tables of visit responses (improvement, deterioration, and no change) for each EORTC QLQ-C30 scale/item score (global health status/QoL, 5 functions, and all symptoms [fatigue, pain, nausea/vomiting, dyspnoea, insomnia, appetite loss, constipation and diarrhoea]) and for each visit will be presented by treatment group.

Change from baseline

Finally, summaries of absolute and change from baseline values of each EORTC QLQ-C30 scale/item will be reported by visit for each treatment group.

Compliance

Compliance with the QLQ-C30 will be presented for each visit and overall.

4.2.4.8.2 EORTC QLQ-BR23

EORTC QLQ-BR23 analyses will be produced for FAS and may be repeated in the *PIK3CA/AKT1/PTEN*-altered population, both populations including patients whose tumours harbour a qualifying *PIK3CA/AKT1/PTEN*-alteration and have an evaluable baseline assessment and at least one evaluable post-baseline assessment, where appropriate.

Time to deterioration

Additional analyses of symptoms, functions will focus on time to deterioration (TTD), which will be analysed for FAS and in *PIK3CA/AKT1/PTEN*-altered population using a stratified log-rank test as described for the PFS and OS endpoints (Section 4.2.3 and Section 4.2.4.1). Separate analyses will be conducted for body image, sexual functioning, sexual enjoyment, future perspective, systemic therapy side effects, breast symptoms, arm symptoms, upset by hair loss. The effect of capivasertib + fulvestrant vs placebo + fulvestrant will be estimated by the HR together with its corresponding CI and p-value. A forest plot by scale/item will also be produced with the hazard ratio estimates, and the associated 95% CI. Summaries of the number and percentage of patients who have an event as well as who were censored will be provided along with the medians for each treatment.

Patients with no evaluable baseline or a baseline score that cannot be deteriorated will be excluded from this analysis.

If there are too few events available for a meaningful analysis of a particular population (it is not considered appropriate to present analyses where there are less than 20 events across both treatment groups within a subgroup), the HR and CI will not be produced for that population. In this case, only descriptive summaries will be provided.

Response by visit

Summary tables of visit responses (improvement, deterioration, and no change) for each EORTC QLQ-BR23 scale/item score and for each visit will be presented by treatment group.

Change from baseline

As described for the EORTC QLQ-C30, summaries of absolute and change from baseline values of each EORTC QLQ-BR23 scale/item will be reported by visit for each treatment group.

Compliance

Compliance with the QLQ-BR23 will be presented for each visit and overall.

CCI [redacted]


CCI
CCI

CCI

[redacted]

4.2.6 Healthcare resource use

Descriptive statistics (as appropriate, including means, median, standard deviation, ranges or frequencies, and percentages) will be provided for each arm on the different types of hospital admissions, the length of stay of people admitted in to the hospital for at least 1 overnight stay and the length of stay of people admitted to the intensive care/high dependency units, as well as the primary sign or symptom the patient presents with. The tables will be produced using the FAS and the *PIK3CA/AKT1/PTEN*-altered subgroup.

To support submissions to payers, additional analyses may be undertaken, and these will be outlined in a separate Payer Analysis Plan.

4.2.7 Safety data

Safety and tolerability data from all cycles of treatment will be combined and will be presented by treatment arm using the Safety analysis set. Additional safety summaries will be provided for the Altered Subgroup Safety Analysis Set. Safety summaries will be descriptive only. No formal statistical analyses will be performed on the safety variables.

The following sections describe the planned safety summaries for AEs, vital signs, laboratory parameters, ECG and WHO performance status. However, additional safety summaries (not specified in this SAP) may need to be produced to aid interpretation of the safety data.

4.2.7.1 Adverse events

All AEs, both in terms of current MedDRA preferred term and CTCAE grade, will be summarised descriptively by count (n) and percentage (%) for each treatment group. Any AE occurring before randomised treatment (i.e. before the administration of the first dose on Study Day 1) will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as 'pre-treatment'. However, any AE occurring before the administration of the first dose on Study Day 1 that increases in severity after the first dose will be regarded as treatment emergent and thus will be included in the summary tables. Note: If an AE is not worse than baseline (pre-dose) severity then it will not be classified as TEAE.

AEs observed up until 30 days (+ 7 days) following last dose of the study treatment will be used for reporting of all the AE summary tables.

All reported AEs will be listed along with the date of onset, date of resolution (if AE is resolved) and investigator's assessment of severity and relationship to study drug. Frequencies and percentages of patients reporting each preferred term (PT) will be presented (i.e. multiple events per patient will not be accounted for apart from on the episode level summaries which may be produced).

Summary information (the number and percent of patients by system organ class (SOC) and PT separated by treatment group) will be tabulated including but not limited to the following:

- All AEs
- All AEs possibly related to capivasertib/placebo only (as determined by the reporting investigator)
- All AEs possibly related to fulvestrant only (as determined by the reporting investigator)
- All AEs possibly related to both capivasertib/placebo and fulvestrant (as determined by the reporting investigator)
- AEs with CTCAE grade 3 or higher
- AEs with CTCAE grade 3 or higher, possibly related to capivasertib/placebo only (as determined by the reporting investigator)
- AEs with CTCAE grade 3 or higher, possibly related to fulvestrant only (as determined by the reporting investigator)
- AEs with CTCAE grade 3 or higher, possibly related to both capivasertib/placebo and fulvestrant (as determined by the reporting investigator)
- AEs with outcome of death
- AEs with outcome of death possibly related to capivasertib/placebo only (as determined by the reporting investigator)

- AEs with outcome of death possibly related to fulvestrant only (as determined by the reporting investigator)
- AEs with outcome of death possibly related to both capivasertib/placebo and fulvestrant (as determined by the reporting investigator)
- All SAEs
- All SAEs possibly related to capivasertib/placebo only (as determined by the reporting investigator)
- All SAEs possibly related to fulvestrant only (as determined by the reporting investigator)
- All SAEs possibly related to both capivasertib/placebo and fulvestrant (as determined by the reporting investigator)
- AEs leading to discontinuation of capivasertib/placebo only
- AEs leading to discontinuation of fulvestrant only
- AEs leading to discontinuation of both capivasertib/placebo and fulvestrant
- AEs leading to dose interruption of capivasertib/placebo only
- AEs leading to dose interruption of fulvestrant only
- AEs leading to dose interruption of both capivasertib/placebo and fulvestrant
- AEs leading to dose reduction of capivasertib/placebo only
- AEs leading to dose modification of capivasertib/placebo
- AEs leading to dose modification or discontinuation of capivasertib/placebo
- Other significant AEs
- Other significant AEs possibly related to capivasertib/placebo only
- Other significant AEs possibly related to both capivasertib/placebo and fulvestrant

All AEs in patients with any confirmed or suspected COVID-19 infection will be listed.

An overall summary of the number and percentage of patients in each category will be presented in the overall safety and in the altered safety populations. For the truncated AE tables of most common AEs, all events that occur in at least 5% of patients overall will be summarised by preferred term, by decreasing frequency. This cut-off may be modified after review of the data. When applying a cut-off (e.g., 5%), the raw percentage should be compared to the cut-off, no rounding should be applied first (i.e., an AE with frequency 4.9% will not appear if the cut-off is 5%).

Each AE event rate (per 100 patient years) will also be summarised by preferred term within each system organ class for the output summarising all AEs. For each preferred term, the event rate is defined as the number of patients with that AE divided by the total treatment duration (days) of randomised treatment summed over patients and then multiplied by 365.25 x 100 to present in terms of per 100 patient years.

Event level summaries of all AEs by SOC and PT will also be produced.

AEs will be assigned CTCAE grades and summaries of the number and percentage of patients will be provided by maximum reported CTCAE grade during the on treatment period, system organ class and preferred term.

For each AE, time to first onset of the AE from date of first dose will be presented in the listing.

Deaths

A summary of deaths will be provided with number and percentage of patients, categorised as:

- Total number of deaths (regardless of date of death)
- Death related to disease under investigation only
- AE outcome of death only
- AE with outcome of death and death related to disease under investigation
- AE outcome of death only and AE onset date falling after 30 (+ 7) days following last dose of study treatment
- AE defined as confirmed or suspected COVID-19 infection leading to death
- Any confirmed or suspected COVID-19 related deaths defined as death due to COVID-19 AE or death in patients with confirmed or suspected COVID-19 infection
- Other deaths

A corresponding listing will also be produced.

4.2.7.2 Adverse events of special interest (AESI)

Preferred terms used to identify AESI, as defined in Section 3.5.6 will be listed before database lock (DBL) and documented in the Trial Master File. Grouped summary tables for certain MedDRA preferred terms will be produced and may also show the individual preferred terms which constitute each AESI grouping. For each grouped AE category, the number (%) of patients experiencing any of the specified terms will be presented. Groupings will be based on preferred terms provided by the medical team prior to DBL, and a listing of the preferred terms in each grouping will be provided.

A table characterizing aspects of each AESI will be provided. This may include but not limited to number of patients experiencing the AESI, the number of serious AESI, CTCAE grade frequencies, time to onset, dose modifications and outcomes related to the AESI.

A summary of total duration (days) of AESI will be provided for events which have an end date, and this may be supported by summaries of ongoing AESI at death and, separately, at

data cut-off. For patients with multiple AESIs within the same PT, the first occurrence of AESI will be used for the analysis.

The overall summary for all AEs reporting the number and percentage of patients in each category will be repeated for diarrhoea and hyperglycaemia events. In addition, for diarrhoea events the number of patients with any diarrhoea AE occurring only on dosing days and occurring only on off days along with the total number of diarrhoea events patients experienced will be presented.

The following characteristics of diarrhoea AEs will also be summarised separately for events on dosing days and on off dosing days:

- Duration of events for on dosing days only (days)
- Pattern of event (intermittent / continuous)
- Number of individual diarrhoea periods for intermittent events only
- Duration of max CTCAE grade diarrhoea period for intermittent events only (days)

4.2.7.3 Summary of long-term tolerability

To assess the long-term tolerability, if there are sufficient patients with events to warrant it, prevalence plots, life table plots and cumulative incidence plots may be presented for each of the AESI grouped terms and any other events considered important after review of the safety data, provided there are ≥ 10 events, that is 10 events per treatment group.

A prevalence plot provides information on the extent to which the events may be an ongoing burden to patients. The prevalence at time *t* after the first dose of study treatment is calculated as the number of patients experiencing the event divided by the number of patients receiving study treatment or in the safety follow-up at time *t*: generally, *t* is categorised by each day after dosing. The prevalence over time may be plotted and presented. Multiple occurrences of the same event are considered for each patient, but a patient is only counted in the numerator whilst they are experiencing one of the occurrences of the event. These plots may only be produced for AESI that have ≥ 10 events, that is 10 events per treatment group.

A life table can be used to describe the time to onset (date of onset – start date of treatment + 1) of the event and specifically when patients are most at risk of first experiencing the event. The hazard, or in other words the probability of having and AE in a specific time-period (e.g., 0 – 1 months, 1 – 3 months, 3 – 6 months, etc.) given that the patient reaches the time-period without having an event is plotted for each time-period. These plots may only be produced for AESI that have ≥ 10 events, that is 10 events per treatment group.

A cumulative incidence plot is a plot of the raw cumulative incidence and cumulative incidence function over time, these may be presented on separate plots. The raw cumulative

incidence is the actual probability that a patient will have experienced their first occurrence of the event at a given time-point. These plots may only be produced for AESI that have ≥ 10 events, that is 10 events per treatment group.

4.2.7.4 Exposure

Exposure will be summarised for the Safety analysis set.

The following summaries will be produced:

- Total exposure
- Actual exposure (capivasertib or matching placebo, fulvestrant)
- RDI (capivasertib or matching placebo, fulvestrant)
- Number of cycles received (capivasertib or matching placebo, fulvestrant)
- Summary of duration of exposure (capivasertib or matching placebo, fulvestrant)
- Summary of interruptions and reductions and delays for capivasertib or matching placebo, fulvestrant. Dose interruptions will be based on investigator dosing decisions
- Summary of duration of exposure (capivasertib or matching placebo, fulvestrant) will summarized for altered safety analysis set

4.2.7.5 Safety endpoints supporting the dose

Cumulative incidence plots will be used to summarize the safety endpoints supporting the dose.

A stacked column plot will be used to illustrate the profile of dose changes over time for the capivasertib + fulvestrant arm.

Further analyses may be explored to further investigate the possible impact of competing risks on the analyses of these endpoints.

Overdose

A summary characterizing overdoses of capivasertib for patients in capivasertib + fulvestrant arm only will be provided. This will include the number of patients experiencing an overdose, summary statistics on the number of overdoses per patient, the number of patients with an overdose leading to an AE and the time to first overdose.

4.2.7.6 Laboratory measurements

Laboratory data obtained until 30 days (+ 7 days) after the last dose of study treatment will be used for reporting.

Data summaries and listings will be provided by AstraZeneca preferred units.

All laboratory data will be listed. Flags will be applied to values falling outside – reference ranges (which will be explicitly noted on these listings where applicable), and to values for which CTCAE grading applies.

Scatter plots (shift plots) of baseline to maximum/minimum values (as appropriate) on treatment (i.e., on treatment is defined as data collected between the start of treatment and the relevant follow-up period following the last dose of study treatment) may be produced for certain parameters if warranted after data review.

Box-plots of absolute values by week, and box-plots of change from baseline by week, may be presented for certain parameters if warranted after data review.

Shift tables of laboratory values by worst common toxicity criteria (CTCAE) grade will be produced, and for specific parameters shift tables indicating hyper- and hypo- directionality of change will be produced. The laboratory parameters for which CTCAE grade shift outputs will be produced are:

- Haematology: Haemoglobin (low and high), Leukocytes (low and high), Lymphocytes (absolute count), Neutrophils (absolute count), Platelets
- Clinical Chemistry: ALT, AST, Albumin, Alkaline Phosphatase (ALP), Total bilirubin, Magnesium (hypo- and hyper-), Sodium (hypo- and hyper-), Potassium (hypo- and hyper-), Corrected Calcium (hypo- and hyper-), Creatinine, Fasted Glucose (CTCAE v4, hypo- and hyper-) and non-fasted glucose (CTCAE v4, hypo- and hyper-).

For parameters with no CTCAE grading that are listed in the CSP, shift tables from baseline to worst value on treatment will be provided. Additional summaries will include a shift table of urinalysis (Glucose, Blood, Ketones, Protein) comparing baseline value to maximum on treatment value.

Summary of clinically important maximum changes in blood chemistry and haematology will also be produced.

The denominator used in laboratory summaries of CTCAE grades will only include evaluable patients. If a CTCAE criterion involved a change from baseline, evaluable patients are those who have both a pre-dose and at least 1 post-dose value recorded. If a CTCAE criterion does not consider changes from baseline. Evaluable patients are those who have at least 1 post-dose value recorded.

Summary statistics on the cycle 1 day 1 pre-dose and cycle 1 day 1 4 hours post dose glucose assessments will be produced.

Liver Laboratory Assessments

The following summaries will include the number (%) of patients who have elevated ALT, AST, and total bilirubin during the study independently of causality attribution:

- ALT ≥ 3x – ≤ 5x, > 5x- ≤ 20x and > 20x ULN during the study
- AST ≥ 3x – ≤ 5x, > 5x – ≤ 20x, and > 20x ULN during the study
- Total bilirubin ≥ 2x – ≤ 3x, > 3x – ≤ 5x, > 5x ULN during the study
- ALT or AST ≥ 3x – ≤ 5x, > 5x – ≤ 20x, > 20x ULN during the study
- ALT or AST ≥ 3x ULN and total bilirubin ≥ 2x ULN during the study (potential Hy's law): the onset date of ALT or AST elevation should be prior to or on the date of total bilirubin elevation
- ALT or AST ≥ 3x ULN, and ALP ≥ ULN and total bilirubin ≥ 2x ULN during the study (potential Hy's law): the onset date of ALT or AST elevation should be prior to or on the date of total bilirubin elevation

Narratives will be provided in the CSR for patients who have ALT ≥ 3x ULN plus total bilirubin ≥ 2x ULN or AST ≥ 3x ULN plus total bilirubin ≥ 2x ULN with the onset date of ALT or AST elevation prior to or on the date of total bilirubin elevation.

Liver biochemistry test results over time for patients with elevated ALT (i.e. ≥ 3x ULN) or AST (i.e. ≥ 3x ULN), and elevated total bilirubin (i.e. ≥ 2x ULN) (where the onset date of ALT or AST elevation should be prior to or on the date of total bilirubin elevation) will be plotted.

Individual patient data where ALT or AST, and ALP, and total bilirubin are elevated at any time will be listed also.

Plots of maximum post-baseline ALT and AST vs. maximum post-baseline total bilirubin, expressed as multiples of ULN, will also be produced with reference lines at 3×ULN for ALT and AST, and 2×ULN for Total bilirubin. In each plot, total bilirubin will be in the vertical axis.

Abnormal Thyroid function

Elevated thyroid stimulating hormone (TSH) and thyroxine will be summarised per treatment group in terms of number (%) of patients with elevated values (higher than the upper normal range), low values (lower than lower normal range), elevated values post-dose and within normal range at baseline, low values post-dose and within normal range at baseline. Shift tables showing baseline to maximum and baseline to minimum will be produced.

4.2.7.7 Vital signs

Summaries for vital signs data will include all data obtained until 30 days (+ 7 days) after the last dose of study treatment. Absolute values and change from baseline for diastolic and systolic blood pressure (BP), pulse, respiratory rate, temperature and weight will be summarised at each visit. The denominator in vital sign data should include only those patients with recorded data.

Box plots for absolute values and change from baseline by week may be presented for certain vital signs parameters if warranted after data review.

4.2.7.8 Physical examinations

Individual physical examination data will not be summarised.

4.2.7.9 Electrocardiograms (ECGs)

The average value of the ECG triplicates and LVEF collected at each visit for VHP countries until the safety follow-up will be included in the summary tables. Absolute values and change from baseline for ECG heart rate, PR duration, QRS duration, QT duration, QTcF duration and RR duration may be presented.

The following summaries for QTcF should also be included:

Absolute QTcF interval prolongation:

- QTcF interval > 450 milliseconds
- QTcF interval > 480 milliseconds
- QTcF interval > 500 milliseconds

Change from baseline in QTcF interval:

- QTcF interval increases from baseline > 30 milliseconds
- QTcF interval increase from baseline > 60 milliseconds

Overall evaluation of ECG is collected in terms of normal or abnormal, and the relevance of the abnormality is termed as “clinically significant” or “not clinically significant”. ECG evaluations will be summarised using a shift table of baseline to worst evaluation on-treatment during the study if a sufficient number of ECG assessments are recorded. ECG data will be listed.

4.2.7.10 Echocardiograms (ECHOs/LVEF)

ECHO (LVEF) recorded at each visit will be summarised. For VHP countries only, change from baseline results will be summarised over the scheduled time points.

4.2.7.11 WHO/ECOG performance status

All WHO/ECOG PS data will be summarised over time. Absolute values and change from baseline for WHO/ECOG PS will be summarised at each visit.

4.2.8 Pharmacokinetic data

PK analyses will be performed based on the PK Analysis Set. Any exclusion of plasma concentration data from the analysis will be documented and justified, but all values will be listed.

PK concentration data will be tabulated by nominal time using standard summary statistics (geometric mean, geometric coefficient of variation, arithmetic mean, standard deviation, median, minimum, maximum and n).

The plasma concentration-time data will be analysed by population PK methods using a non-linear mixed-effects modelling approach. The actual sampling times will be used in these calculations. PK parameters, including variability parameters, will be estimated as data permits. The influence of intrinsic (e.g., ethnicity, sex, age, weight, renal function and hepatic function) and extrinsic (e.g., concomitant medication) factors on the PK will be evaluated and exposure-response relationships explored. Data from this study may be pooled with data from other studies. Details will be outlined in a separate modelling analysis plan and results may be reported outside of the CSR.

In addition, the area under the plasma concentration versus time curve ($AUC_{0\text{-}12h}$), the observed maximum concentration (C_{max}), and the time of Cmax (t_{max}) will be derived in the subgroup of approximately 6 Japanese patients with rich capivasertib PK data (Japan Intensive Pharmacokinetic (PK) Analysis Set).

4.2.9 Biomarkers

Additional summaries and analyses not mentioned in Section 4.2.3.2 CCI [redacted]

4.2.10 Demographic, initial diagnosis and baseline characteristics data

The following will be summarized for all patients in the FAS and altered subgroup FAS unless specified otherwise, by treatment group:

- Patient disposition (including screening failures, reason for screening failure and study treatment discontinuation and study withdrawals due to COVID-19 infection) – in all patients
- Important protocol deviations
- Inclusion in analysis sets – in all randomized patients
- Demographics (age, age group [< 50, ≥ 50 - < 65, ≥ 65 - < 75 and ≥ 75 years], sex, race and ethnicity) – in FAS only
- Patient characteristics at baseline (height, weight, weight group, BMI and BMI group)
- Patient recruitment by region, country and centre

- Previous disease-related treatment modalities
- Disease characteristics at baseline (including, but not limited to, stratification factors, extent of disease, measurability, ECOG performance status, primary tumour location, tumour grade, AJCC staging at diagnosis, histology type, overall disease classification at study entry (metastatic or locally advanced), number of metastatic sites at baseline, menopausal status, type of endocrine resistance, prior CDK 4/6 (yes/no), reasons for not receiving CDK 4/6 prior treatment, BRCA status, if known and diabetic status, if known)
- Hormone receptor status
- Prior (neo)adjuvant chemotherapy (Y/N)
- Prior lines of endocrine based therapy for locally advanced (inoperable) or metastatic disease (0, 1 or 2)
- Prior lines of therapy for locally advanced (inoperable) or metastatic disease (includes endocrine and chemotherapy) (0, 1, 2, 3)
- Extent of disease at baseline
- Tumour, nodes, metastases (TNM) classification at initial diagnosis
- Disease related medical history (past and current)
- Relevant surgical history
- Disallowed concomitant medications
- Allowed concomitant medications
- Post-discontinuation cancer therapy

The following summaries and corresponding listings in patients with confirmed or suspected COVID-19 infection for all patients in the FAS will be provided:

- Previous and concurrent medical history
- Demographic and baseline characteristics

The medications will be coded following AstraZeneca standard drug dictionary/WHO Drug dictionary as applicable.

4.2.11 Concomitant and other treatments

Concomitant medications and procedures will be summarised by treatment arm, therapeutic subgroup (ATC 2nd level), chemical subgroup (ATC 4th level) and preferred WHO name for the FAS. Patients with the same concomitant medication/procedure multiple times will be counted once per medication/procedure. A medication/procedure that can be classified into more than once chemical and/or therapeutic subgroup will be presented in each subgroup.

5 INTERIM ANALYSES

5.1 Analysis methods

The OS Interim Analysis is expected to occur when approximately 394 OS events have been observed in the overall population and similar maturity has been reached in the *PIK3CA/AKT1/PTEN*-altered population (56% maturity, 80% information fraction). The significance level for OS will be based on the significance level available after the PFS primary analysis and will be determined according to the O'Brien and Fleming method (Lan and DeMets 1983).

Following FDA advice, a small alpha spend will be applied to the analysis of no OS detriment assessed at the time of the PFS primary analysis. This will use a bespoke alpha spending function with 0.0001 alpha assigned to DCO1 in each of the overall and *PIK3CA/AKT1/PTEN*-altered populations. The OS interim analyses will use the planned cumulative alpha at DCO2 from the 2-look O'Brien & Fleming method.

5.2 Independent Data Monitoring Committee

This study will use an external Independent Data Monitoring Committee (IDMC) to assess ongoing safety analyses prior to the PFS primary analysis database lock. The committee will meet approximately 7 months after the study has started to review the safety data from the study. The IDMC will meet at least every 6 months thereafter. Following each meeting, the IDMC will report to the sponsor and may recommend changes in the conduct of the study.

This committee will be composed of therapeutic area experts and biostatisticians, who are not employed by AstraZeneca and are free from conflict of interest.

Following the reviews, the IDMC will recommend whether the study should continue unchanged, be stopped, or be modified in any way. Once the IDMC has reached a recommendation, a report will be provided to AstraZeneca. The report will include the recommendation and any potential protocol amendments and will not contain any unblinding information.

The final decision to modify or stop the study will sit with the sponsor. The sponsor or IDMC may call additional meetings if at any time there is concern about the safety of the study.

Full details of the IDMC procedures and processes can be found in the IDMC Charter. The safety of all AstraZeneca/MedImmune clinical studies is closely monitored on an ongoing basis by AstraZeneca/MedImmune representatives in consultation with the Patient Safety Department. Issues identified will be addressed; this could involve, for instance, amendments to the Clinical Study Protocol and letters to investigators.

6 CHANGES OF ANALYSIS FROM PROTOCOL

Following FDA advice, a small alpha spend will be applied to the analysis of no OS detriment assessed at the time of the PFS primary analysis. This will use a bespoke alpha spending function with 0.0001 alpha assigned to DCO1 in each of the overall and *PIK3CA/AKT1/PTEN*-altered populations. The remaining OS analyses will use the planned cumulative alpha at DCO2 and DCO3 from the 2-look O'Brien & Fleming method.

7 REFERENCES

Breslow NE 1974
Breslow, NE. Covariance Analysis of Censored Survival Data. Biometrics. 1974; 30:89–99.

Burman et al 2009
Burman CF, Sonesson C, Guilbaud O. A recycling framework for the construction of Bonferroni-based multiple tests. Stat Med 2009;28:739–61.

Carr et al 2016
Carr TH, McEwen R, Dougherty B, Johnson JH, Dry JR, Lai Z, et al. Defining actionable mutations for oncology therapeutic development. Nat Rev Cancer 2016 Apr 26;16(5):319-29.

Cox DR 1972
Cox DR. Regression Models and Life-Tables, Journal of the Royal Statistical Society. Series B (Methodological), Vol. 34, No. 2. (1972), pp. 187-220.

Cristofanilli et al 2016
Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17:425-39.

Curtis et al 2012
Curtis C, Shah SP, Chin SF, Turashvili G, Rueda OM, Dunning MJ, etal. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature 2012;486:346-52.

Di Leo et al 2018
Di Leo A, Johnston S, Lee KS, Ciruelos E, Lønning PE, Janni W, et al. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2018;19:87-100.

Fayers et al 2001

Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer; 2001.

Fleischer F et al 2011

Fleischer F, Gaschler-Markefski B, Bluhmki E. How is retrospective independent review influenced by investigator-introduced informative censoring: A quantitative approach. Stat Med. 2011; 30(29):3373-86

Hammond et al 2010

Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. JClin Oncol 2010;28:2784-95; erratum in J Clin Oncol 2010;28:3543.

Hortobagyi et al 2016

Hortobagyi GN, Chen D, Piccart M, Rugo HS, Burris HA III, Pritchard KI, et al. Correlative analysis of genetic alterations and everolimus benefit in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Results From BOLERO-2. J Clin Oncol 2016;34:419-26.

Lan and DeMets 1983

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659–63.

Magirr Burman 2019

Magirr D, Burman C-F. Modestly weighted logrank tests. Statistics in Medicine. 2019;1–9

Osoba D et al 1998

Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998;16(1):139–144.

Pereira et al 2016

Pereira B, Chin SF, Rueda OM, Vollan HK, Provenzano E, Bardwell HA, et al. The somatic mutation profiles of 2,433 breast cancers refines their genomic and transcriptomic landscapes. Nat Commun 2016;7:11479. doi: 10.1038/ncomms11479.

Spiessens and Debois 2010

Spiessens B, Debois M. Adjusted significance levels for subgroup analyses in clinical trials. Contemp Clin Trials 2010;31:647-56.

Spoerke et al 2016

Spoerke JM, Gendreau S, Walter K, Qui J, Wilson TR, Savage H, et al. Heterogeneity and clinical significance of ESR1 mutations in ER-positive metastatic breast cancer patients receiving fulvestrant. Nat Commun 2016;7:11579. doi: 10.1038/ncomms11579.

Sprangers et al 1996

Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996;14:2756–68.

Sun X, Chen C. 2010

Sun X, Chen C. Comparison of Finkelstein's Method With the Conventional Approach for Interval-Censored Data Analysis. Stat Biopharm Res. 2010; 2:97-108

Van Hout, 2012

Van Hout B, Janssen MF, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012; 15(5):708-15.

Wolff et al 2018

Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med2018;142:1364-82.

8 APPENDICES

Appendix A Schedule of Activities (SoA)

	Screen	Cycle 1[a]			Cycle 2[a, c]		Cycle 3[a, c] →	Discontinuation[v]		Post-treatment follow-up	Progres-sion	Survival follow-up	Details in CSP section or appendix
								Fulvestrant	Capivasertib/ placebo	30 days after last dose		Every 8 weeks	
Week		**1**	**3**		**1**	**3**	**1**						
Day of week	**-28 to 0**	**1**	**1**	**4**	**1**	**1**	**1**						
Visit window (days)[b]		**0**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**+7**	**+7**	**+7**	**+7**	**±7**	
Informed consent	X												Section 5.1 Appendix C
Inclusion/exclusion criteria	X												Sections 5.1 & 5.2
Prepare ePRO device[d]		X											Section 8.1.7.8
Train patient on ePRO device[e]		X											Section 8.1.7.8
Routine clinical procedures[f]													
Demography/baseline characteristics	X												
Medical/surgical history	X												Sections 5.1 & 5.2
Smoking history	X												
Previous cancer therapy	X												Section 5.2
BRCA1/2 status (local testing), if available	X												
Concomitant medication	X	At every study visit											Section 6.5
ECOG/WHO performance status	X	X	X		X	X	X	X	X	X			Appendix B
Physical examination	X	X			X		X	X	X	X			Section 8.2.2

	Screen	Cycle 1[a]			Cycle 2[a, c]		Cycle 3[a, c] →	Discontinuation[v]		Post-treatment follow-up	Progres-sion	Survival follow-up	Details in CSP section or appendix
								Fulvestrant	Capivasertib/ placebo	30 days after last dose		Every 8 weeks	
Week		**1**	**3**		**1**	**3**	**1**						
Day of week	**-28 to 0**	**1**	**1**	**4**	**1**	**1**	**1**						
Visit window (days)[b]		**0**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	+7	+7	+7	+7	±7	
Vital signs	X	Pre (within 30m) and 1-2h post (±30m)	X		X	X	X	X	X	X			Section 8.2.3
Height	X												Section 8.2.2
Weight	X	X			X		X	X	X	X			Section 8.2.2
12-lead ECG	X	Pre (within 30m) and 1h post (±30m)			Cycle 2, Week 1, Day 1 and every 12 weeks thereafter				X				Section 8.2.4
MUGA/ECHO (LVEF)[g]	X	As clinically indicated during study treatment											Section 8.2.5
Routine safety measurements[f]													
Adverse events	X	At every study visit											Section 8.3 Appendix E
Pregnancy test (peri-/pre-menopausal only)	X	X	As clinically indicated and at treatment discontinuation										Section 8.4.2
Oestradiol and FSH[h]	X	X			X		X						Section 8.2.1
International Normalised Ratio (INR)	X	As clinically indicated											Section 8.2.1
Haematology[c]	X	Pre	Pre		Pre	Pre	X	X	X				Section 8.2.1

	Screen	Cycle 1[a]			Cycle 2[a, c]		Cycle 3[a, c] →	Discontinuation[v]		Post-treatment follow-up	Progres-sion	Survival follow-up	Details in CSP section or appendix
								Fulvestrant	Capivasertib/ placebo	30 days after last dose		Every 8 weeks	
Week		**1**	**3**		**1**	**3**	**1**						
Day of week	**-28 to 0**	**1**	**1**	**4**	**1**	**1**	**1**						
Visit window (days)[b]		**0**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**+7**	**+7**	**+7**	**+7**	**±7**	
Clinical chemistry[c,i]	X	Pre	Pre		Pre	Pre	X	X	X				Section 8.2.1
Urinalysis[c]	X	Pre	Pre		Pre	Pre	X	X	X				Section 8.2.1
Glycosylated haemoglobin (fasting)[c,j]	X	Every 12 weeks from Cycle 1, Week 1, Day 1						X	X				Section 8.2.1
Lipids (fasting)[c,j]	X	Every 12 weeks from Cycle 1, Week 1, Day 1							X				Section 8.2.1
Glucose (fasting)[c,j]	X	Pre (within 3h) and 4h post (±30m)	Pre		Pre		X		X				Section 8.2.1
Biomarker analysis													
FFPE tumour sample[k]	X												Section 8.7.1.1
Single biopsy at disease progression (optional)[l]											X		Section 8.7.1.2
Paired biopsies (optional)[l,m]	X			X									Section 8.7.1.2
ctDNA blood samples[c,l]	X	Pre	Pre		Pre		Pre	X	X		X		Section 8.7.2
Circulating soluble factors blood draw[c,l,n]	X	Pre	Pre		Pre		Pre, C3 only	X	X		X		Section 8.7.2
Whole blood DNA sample (genomic markers)[c,l,n]	X	Pre	Pre		Pre		Pre, C3 only	X	X		X		Section 8.7.2

	Screen	Cycle 1[a]			Cycle 2[a, c]		Cycle 3[a, c] →	Discontinuation[v]		Post-treatment follow-up	Progres-sion	Survival follow-up	Details in CSP section or appendix
								Fulvestrant	Capivasertib/ placebo	30 days after last dose		Every 8 weeks	
Week		**1**	**3**		**1**	**3**	**1**						
Day of week	**-28 to 0**	**1**	**1**	**4**	**1**	**1**	**1**						
Visit window (days)[b]		**0**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**+7**	**+7**	**+7**	**+7**	**±7**	
Whole blood RNA sample (genomic markers)[c,l,n]	X	Pre	Pre		Pre		Pre, C3 only	X	X		X		Section 8.7.2
Genetic sample (optional)													
Blood sample for pharmacogenetics DNA (optional)[l]	X												Section 8.6
Pharmacokinetic measurements[c]													
Capivasertib PK plasma samples		1h (±10m) and 4h (±30m) post-dose	Pre (<30 m)		Pre (<30 m)	Pre (<30 m)							Section 8.5
Capivasertib PK plasma samples for 12 Japanese patients only		Pre (within 30m) and 0.5 (±5m), 1 (±10m), 2 (±10m), 4 (±30m), 6 (±30m), 8 (±30m), 12h (±1h) post-dose	Pre (<30 m)		Pre (<30 m)	Pre (<30 m)							Section 8.5
Imaging and other assessments													

	Screen	Cycle 1[a]			Cycle 2[a, c]		Cycle 3[a, c] →	Discontinuation[v]		Post-treatment follow-up	Progres-sion	Survival follow-up	Details in CSP section or appendix
								Fulvestrant	Capivasertib/ placebo	30 days after last dose		Every 8 weeks	
Week		**1**	**3**		**1**	**3**	**1**						
Day of week	**-28 to 0**	**1**	**1**	**4**	**1**	**1**	**1**						
Visit window (days)[b]		**0**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**+7**	**+7**	**+7**	**+7**	**±7**	
Bone scan	X	As clinically indicated											Section 8.1.6
RECIST v1.1 tumour assessments[o]	X	Every 8 weeks (±7 days) for the first 18 months and every 12 weeks thereafter, from randomisation to radiological progression. Patients who discontinue treatment prior to progression should continue to be scanned until progression.											Section 8.1.1 & Appendix A
Survival status[p]										X		X	Section 8.1.2
PFS2[q]										X		X	Section 8.1.3
Subsequent cancer therapy following discontinuation of study treatment[q]										X		X	Section 6.7
Patient-reported outcomes and healthcare resource utilisation													
EORTC QLQ-C30		Cycle 1, Week 1, Day 1 (-3 days) and every 4 weeks (±3 days) until PFS2. Also at discontinuation of study treatment visit (+3 days) and, for those who discontinue for reasons other than progression, also at progression visit (+3 days). If PROs have been completed up to 3 days prior to the discontinuation or progression visit, they do not need to be repeated.											Section 8.1.7.1
EORTC QLQ-BR23													Section 8.1.7.2
EQ-5D-5L													Section 8.1.7.3
PGIS													Section 8.1.7.4
PGIC					Every 4 weeks (±3 days) after Cycle 1, Week 1, Day 1 until PFS2. Also at discontinuation of study treatment visit (+3 days) and, for those who discontinue for reasons other than progression, also at progression visit (+3 days). If PROs have been completed up to 3 days prior to discontinuation or progression visit, they do not need to be repeated.									Section 8.1.7.5

	Screen	Cycle 1[a]			Cycle 2[a, c]		Cycle 3[a, c] →	Discontinuation[v]		Post-treatment follow-up	Progres-sion	Survival follow-up	Details in CSP section or appendix
								Fulvestrant	Capivasertib/ placebo	30 days after last dose		Every 8 weeks	
Week		**1**	**3**		**1**	**3**	**1**						
Day of week	**-28 to 0**	**1**	**1**	**4**	**1**	**1**	**1**						
Visit window (days)[b]		**0**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**+7**	**+7**	**+7**	**+7**	**±7**	
PGI-TT		Cycle 1, Week 1, Day 1 (-3 days) and every 2 weeks (±2 days) up to and including Week 12 and then every 4 weeks (±3 days) until discontinuation of study treatment, at discontinuation of study treatment visit (+3 days) and at 4 weeks (±3 days) post discontinuation of study treatment visit. If PROs have been completed up to 3 days prior to discontinuation visit, they do not need to be repeated.											Section 8.1.7.6
PRO-CTCAE													Section 8.1.7.7
Healthcare resource use (HOSPAD)[r]		Healthcare resource use module is event driven and should be populated as required at every study visit											Section 8.8
Study treatment administration													
Randomisation[s]		X											Section 6.3
Fulvestrant dosing		X	X		X		X						Section 6.1.2
Capivasertib/placebo dosing[t]		Twice daily on days 1 to 4 every week (ie, 4 days on and 3 days off). A minimum interval of 3 days is required between the last dose of the previous week of treatment and the first dose of the following week of treatment											Section 6.1.1
LHRH agonist dosing (for pre-/peri-menopausal women only; both treatment arms)	X[u]	Sub-cutaneous administration every 28 days or as per manufacturer's instructions											Sections 5.1, 5.3.3.1 and 6.5.1

NOTE: Unscheduled visits may be initiated as needed. Only required assessments are to be performed as per investigator's discretion.

[a] Specified times (eg, 'Pre', '1-2h post', '4h post', etc) refer to capivasertib/placebo dosing.

[b] Study visits are scheduled relative to Week 1, Day 1 of each cycle. As per protocol, the visit window is -1/+3 days for most visits, however. a -1 day window cannot be used for study treatment dosing and should only be used for labs and other assessments.

[c] Screening laboratory assessments taken within 3 days of Cycle 1, Day 1 do not need to be repeated and can be utilised for Cycle 1, Day 1/randomisation. Laboratory safety assessments, the collection of blood samples for biomarker analysis (ctDNA sample, circulating soluble factors sample, whole blood DNA sample and whole blood RNA sample) and rich PK sampling should be performed on the day of the scheduled study visit. However, from Cycle 2 onwards, the laboratory safety assessments and biomarker sampling may be performed 1 day before the scheduled study visit. These samples must be collected pre-dosing.

[d] The handheld device must be charged and fully functional at the beginning of the baseline visit to ensure that the PROs can be completed at the start of the visit.

[e] The patient should be trained on the use of the device and the importance of completing the PRO questionnaires in accordance with the schedule throughout the study.

[f] Routine safety measurements and routine clinical procedures should be performed before dosing of study treatment unless otherwise specified.

[g] Bidimensional ECHO is the preferred modality because of the global technetium [Tc-99m] shortage (but MUGA can be used alternatively). The modality of the cardiac function assessments must be consistent within patient ie, if ECHO is used for the screening assessment and a follow-up assessment if clinically indicated, then ECHO should also be used for subsequent scans if required. Patients should also be examined using the same machine and operator whenever possible.

[h] Female pre- and peri-menopausal patients starting an LHRH agonist (either starting or continuing this treatment) must have oestradiol and FSH measurements done at screening (before Cycle 1, Day 1) and after at least 4 weeks after commencing LHRH agonist treatment to confirm post-menopausal levels; assessments after screening will be at Day 1 of each cycle and when clinically indicated. Female patients <60 years who are considered post-menopausal per wording of inclusion criterion 5, must have oestradiol and FSH levels confirmed as being within the standard laboratory reference range for post-menopausal females at screening (before Cycle 1, Day 1) only and if clinically indicated (see Section 8.2.1 for all details when and for whom FSH and oestradiol must be checked).

[i] For patients taking concomitant metformin, please refer to Sections 8.2.1.2 and 8.4.5.3.

[j] 'Fasting' is defined as no caloric intake for ≥4 hours before sampling. Glucose samples should be done under fasting conditions with the exception of the 4-hour post dose sample on Cycle 1, Week 1, Day 1 which can be fasting or non-fasting.

[k] FFPE tumour sample: Tumour tissue will be required at baseline for determination of *PIK3CA/AKT1/PTEN* status at a central laboratory to allow monitoring of the prevalence of the *PIK3CA/AKT1/PTEN*-altered subgroup. Tumour tissue samples will be collected as detailed in the Laboratory Manual and Diagnostic Testing Manual. The most recently collected tumour tissue, from primary or recurrent cancer is required. FFPE blocks are strongly preferred. If not possible, preferably 30 (minimum 20) freshly-cut unstained serial tumour tissue sections are accepted provided they met the specifications described in the Diagnostic Testing Manual. Local pathology QC must be completed prior to randomisation to ensure the sample is suitable for NGS analysis, based on the requirements described in the Diagnostic Testing Manual.

[l] These samples will not be collected in China. Results can be provided to the investigator upon request, if available.

[m] Paired biopsies (optional): Baseline sample: at screening OR pre-dose on Cycle 1, Week 1, Day 1. On-treatment sample: at Cycle 1, Week 3, Day 4 (any day between Cycle 1, Week 3, Day 2 and Cycle 1, Week 3, Day 4 is allowed) >4 hours post-dose.

[n] Circulating soluble factor, whole blood DNA sample, and whole blood RNA sample draws: To be taken at screening, pre-dose on Cycle 1, Week 1, Day 1; Cycle 1, Week 3, Day 1; Cycle 2, Week 1, Day 1; Cycle 3, Week 1, Day 1, at progression, and at discontinuation of IMP if this falls on a different visit/time than progression.

[o] Baseline RECIST v1.1 assessments will be performed using CT scans of the chest, abdomen and pelvis (or MRI where CT is contraindicated) and should be performed as close as possible to the start of treatment. RECIST v1.1 follow-up assessments will include CT scans of thorax, abdomen and pelvis (or MRI where CT is contraindicated) for all patients. Any other sites at which new disease is suspected should also be appropriately imaged.

[p] In addition to regular contacts at ≤8-week intervals, patients will be contacted in the 7 days following a specified date (data cut-off date) for survival analysis.

[q] Patients will enter the PFS2 follow-up period once the patient has discontinued study treatment due to progressive disease by RECIST v1.1. Progression on second-line treatment will be documented by site personnel at the 30-day follow-up visit, every 8 weeks (±7 days) for the first 2 years and every 12 weeks (±7 days) thereafter until second progression. Survival status and subsequent cancer therapies will be documented by site personnel, following objective

disease progression or treatment discontinuation, at the 30-day follow-up, every 8 weeks (±7 days) for the first 2 years and every 12 weeks (±7 days) thereafter until end of study, study withdrawal or death.

[r] Assessments include: number of hospitalisations and attendances; primary symptom/reason associated with hospitalisation or attendance; length of stay, including time in intensive care; and concomitant medication and procedures undertaken.

[s] Randomisation must occur within 28 days of the start of screening. Randomisation and Cycle 1, Week 1, Day 1 should ideally occur on the same day.

[t] Day 1 of each cycle is defined by fulvestrant dosing and fulvestrant should not be delayed due to capivasertib/placebo toxicity. In the case of a capivasertib/placebo dosing delay at the beginning of the cycle, the same routine safety measurements and routine clinical procedures must be repeated on the next planned date of dosing. Cycles are 28-day long, dosing outside of the prespecified window will be considered as overdose except for a dose delay situation.

[u] Administration of LHRH agonist in pre- or peri-menopausal women must start prior to or on Cycle 1, Day 1.

[v] If both drugs are discontinued at the same time as progression, visits are combined and the optional biopsy is completed, if applicable.

→, onwards; BRCA1/2, breast cancer gene 1/2; CT, computed tomography; ctDNA, circulating tumour DNA; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; EORTC QLQ-BR23, EORTC Quality of Life Questionnaire breast cancer specific module; EORTC QLQ-C30, EORTC Quality of Life Questionnaire – Core 30 items; ePRO, electronic patient-reported outcome; EQ-5D-5L, European Quality of Life 5-Domain 5-Level Scale; FFPE, formalin-fixed paraffin-embedded; FSH, follicle stimulating hormone; HOSPAD, Hospital Admission module; LHRH, luteinising-hormone releasing hormone; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition scan; PFS2, time from randomisation to second progression or death; PGIC, Patient Global Impression–Change; PGIS, Patient Global Impression–Severity; PGI-TT, Patient Global Impression–Treatment Tolerability; PK, pharmacokinetics; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PTEN, phosphatase and tensin homolog; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; RNA, ribonucleic acid; WHO, World Health Organisation.

Appendix B Biomarker Definition

Table 20 Biomarker Definition

Gene (Transcript)	Variant Class	Biomarker Rules
AKT1 (NM_001014431)	Short Variant	Any short variant with protein effect E17K
PIK3CA (NM_006218)	Short Variant	Any short variants listed below: CCI [redacted]
PTEN (NM_000314)	Short Variant	Any short variants listed below: CCI [redacted]
		Any nonsense, frameshift, or splice site alteration
PTEN (Any transcript)	Copy Number Alteration	Any homozygous deletion of one or more exons, regardless of transcript
	Rearrangement	Any rearrangement that disrupts protein function, regardless of transcript • Intragenic events including duplications of only part of the gene, deletions, or inversions • Translocations, deletions, or inversions where one breakpoint is in *PTEN* and the other breakpoint is in another gene or intergenic region.

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