25 April 2024
EMA/236868/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Truqap

International non-proprietary name: Capivasertib

Procedure No. EMEA/H/C/006017/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADME	Absorption distribution metabolism excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
AKT	Serine/threonine specific protein kinase
ALP	Alkaline phosphatase
APD	Action potential duration
API	Active pharmaceutical ingredient
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}12h}$	Area under the plasma concentration-time curve from zero to 12 hours
$AUC_{12h,ss}$	Area under the plasma concentration-time curve for 12 hours at steady state
AUC_{inf}	Area under the plasma concentration-time curve from time zero to infinity
BCS	Biopharmaceutics Classification System
BD	Twice daily
BICR	Blinded independent central review
CBR	Clinical benefit rate
CDK	Cyclin-dependent kinase
CDx	Companion diagnostic
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
C_{max}	Maximum observed plasma (peak) drug concentration
$C_{max,ss}$	Maximum concentration at steady state
CMC	Chemistry, manufacturing and controls
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity

DoR	Duration of response
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
EoP2	End of phase II
EORTC QLQ-C30	EORTC Quality of Life Questionnaire-Core 30 items
ER	Oestrogen receptor
ER+	Oestrogen receptor-positive
ESR	Externally sponsored research
EU	European Union
FAS	Full analysis set
FaSSIF	Fasted state simulated intestinal fluid
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FTIH	First time in human
FT-IR	Fourier transform infrared spectroscopy
GCP	Good clinical practice
GLDH	Glutamate dehydrogenase
GMR	Geometric mean ratio
HbA1C	Glycosylated haemoglobin
HER2−	Human epidermal growth factor receptor 2-negative
hERG	Ether-a-go-go-related gene
HR+	Hormone receptor-positive
HRQoL	Health-related quality of life
IC_{50}	Half-maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IDMC	Independent data monitoring committee
IHC	Immunohistochemistry
IM	Intramuscular
HPLC	High performance liquid chromatography

HS-GC	Headspace gas chromatography
ISH-	No evidence of amplification on in situ hybridisation
ITT	Intention to treat
IV	Intravenous
KF	Karl Fischer titration
LC	Liquid chromatography
LDPE	Low density polyethylene
LHRH	Luteinizing hormone releasing hormone
MAA	Marketing Authorisation Application
mCRPC	Metastatic castration-resistant prostate cancer
MRHD	Maximal recommended human dose
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MTP	Multiple testing procedure
NCA	Noncompartmental PK analysis
NCCN	National Comprehensive Cancer Network
NDA	New drug application
NIR	Near infrared spectroscopy
NMR	Nuclear magnetic resonance
NOAEL	No observed adverse effect level
NOR	Normal operating range
NR	Not reported
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
Overnight fast	Fast from 8 hours before to 4 hours after dosing
pAKT	Phosphorylated serine/threonine-specific protein kinase
Partially fasted	Fast from 2 hours before to 1 hour after dosing
PAR	Proven acceptable range
PBPK	Physiologically based pharmacokinetic modelling
PCE	Polychromatic erythrocytes
PD	Pharmacodynamic(s)
PFS	Progression-free survival

PFS2	Time from randomisation to second progression or death
Ph. Eur.	European Pharmacopoeia
PIK3CA	Gene encoding the phosphatidylinositol 3-kinase α catalytic subunit
PI3K	Phosphatidylinositol 3-kinase
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetics
PPI	Proton pump inhibitor
PRO	Patient-reported outcome
PTEN	Phosphatase and tensin homologue
QoL	Quality of life
RECIST v1.1	Response Evaluation Criteria in Solid Tumours version 1.1
RH	Relative humidity
RP2D	Recommended Phase II dose
RTOR	Real-Time Oncology Review
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SERD	Selective oestrogen receptor degrader
SmPC	Summary of product characteristics
TNBC	Triple-negative breast cancer
TX	Toxicokinetic
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
Vs	Versus
WBC	White blood cells
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 20 April 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Capivasertib AstraZeneca AB, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 October 2021.

The applicant applied for the following indication:

Capivasertib is indicated in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer following recurrence or progression on or after an endocrine based regimen (see section 5.1).

1.2. basis, dossier content

The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0214/2019 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance capivasertib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
17/10/2019	EMEA/H/SA/3985/2/2019/III	*Dr Kristian Wennmalm, Dr Paolo Foggi*
17/09/2020	EMEA/H/SA/3985/4/2020/III	*Prof. Dieter Deforce, Dr Olli Tenhunen*

The scientific advice pertained to the following non-clinical, and clinical aspects:

- The proposed toxicology programme, based on ICH S9 guideline principles, to support a MAA in HR+/HER2− advanced breast cancer;
- The design of the planned double-blind, placebo-controlled, randomised, international Phase 3 study (D3615C00001), intended to provide confirmatory evidence of the clinical benefit of capivasertib in combination with fulvestrant vs fulvestrant alone for the treatment of patients with HR+/HER2− locally advanced or metastatic breast cancer, in particular: the choice of the patient population and line of treatment for the proposed indication to address the unmet medical need; the inclusion of both CDK 4/6 inhibitors naïve and pre-treated patients; the choice of placebo plus fulvestrant as comparator; the stratification factors; the targeted magnitude of benefit and maturity of the PFS and OS analyses; the overall multiple testing procedure; the proposed assessment of patient-reported outcomes (PROs) to support a label claim;
- The safety monitoring plan and anticipated safety database.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: Alexandre Moreau

CHMP Peer reviewer(s): N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Sonja Hrabcik

The application was received by the EMA on	20 April 2023
The procedure started on	18 May 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 August 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	29 August 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 August 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 December 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 January 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 February 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanationto be sent to the applicant on	22 February 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 March 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 April 2024
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	19 April 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Truqap on	25 April 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product on	25 April 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant seeks a marketing authorisation) for the medicinal product Truqap (capivasertib) with the following therapeutic indication:

"Truqap is indicated in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer following recurrence or progression on or after an endocrine based regimen (see section 5.1)".

2.1.2. Epidemiology and risk factors

Breast cancer (BC) is the leading cause of cancer in women and the leading cause of cancer deaths in women (Bray et al, *CA*: *A Cancer Journal for Clinicians*, 2018). In men, breast cancer is rare (Siegel et al 2022). The incidence and prevalence of patients with invasive breast cancer, as well as estimates for the prevalence of subjects with Oestrogen receptor positive (ER+)/Human epidermal growth factor receptor 2-negative (HER2-) breast cancer, are presented in the below table.

Table 1 Epidemiology of ER+/HER2- breast cancer (x 1,000)

	US	EU[a]	Japan[a]	Global[a]
Incidence: New yearly cases of invasive breast cancer	253[a], 282[b]	531	92	2,261
Prevalence of invasive breast cancer	1,071[a]	2,138	328	7,791
Prevalence of ER+, HER2- breast cancer (approximately 70% of invasive breast cancer)	750	1,497	230	5,454

Abbreviations: ER+=estrogen receptor positive; EU=European Union; HER2-=human epidermal growth factor receptor 2 negative; SEER=Surveillance, Epidemiology, and End Results; US=United States.

[a] International Agency for Research on Cancer and World Health Organization 2021

[b] National Cancer Institute and Surveillance, Epidemiology, and End Results (SEER) Program 2021

For women diagnosed with early BC (eBC), the 5-year survival probability is ~96% in Europe. However, when metastatic BC (mBC) is diagnosed, the 5-year survival rate is in the range of 38% (Allemani et al, *Lancet*, 2018). About 157,100 women were estimated to have died from breast cancer in the EU in 2020 (Ferlay et al, *International Journal of Cancer*, 2021). In terms of absolute numbers, mBC was still the leading cause of death from all cancers in women, accounting for ~3.6% of all deaths in women and 1.8% of all deaths in Europe in 2015 (Dafni et al, *Breast Care*, 2019).

2.1.3. Biologic features

BC is a heterogeneous disease comprising different subtypes, which can be identified through molecular biomarkers that also act as predictive factors. It is categorised into different histopathologic subtypes based on the expression of the oestrogen receptor (ER), the progesterone receptor (PR), and human epidermal growth factor 2 (HER2) receptor overexpression or gene amplification. Oestrogen receptor (ER), and progesterone receptor (PR) are together referred to as hormone receptor (HR). HR+, HER2-

breast cancer is the most frequent subtype of breast cancer; approximately 70% of all breast cancers are HR+, HER2- (Howlader et al 2014).

ER is a transcription factor that regulates the expression of oestrogen-responsive genes by binding to a specific DNA sequence found in their regulatory regions. Two major isoforms of the oestrogen receptor have been identified, ERα and ERβ: however, the role of ERβ in cancer remains unclear. The two isoforms are encoded by two genes located on different chromosomes (ESR1 on chromosome 6 and ESR2 on chromosome 14) and regulate different specific genes.

Endocrine therapy (ET) comprises different strategies as suppression of oestrogen production or directly targeting the oestrogen receptor (ER):

- Steroidal/nonsteroidal aromatase inhibitors (AI) (e.g. exemestane/letrozole and anastrozole and exemestane) exert their action by blocking androgen to oestrogen conversion, thus lowering the levels of circulating oestradiol (E2) and, therefore, reducing the activation of ER.
- Direct targeting of ERα is achieved by selective oestrogen receptor modulator (SERM) (e.g. tamoxifen) and selective oestrogen receptor degrader (SERD) (e.g. fulvestrant). SERMs compete with oestrogen for ER binding and show mixed agonist/antagonist capabilities in a tissue-specific fashion. Meanwhile, SERDs create an unstable protein complex that induces ER protein degradation via the proteasome.

The AKT serine/threonine protein kinases (AKT1, AKT2, AKT3) are key downstream effectors of the PI3K/AKT/PTEN pathway, promoting cell proliferation, survival, metabolism, and gene expression (Brown and Banerji 2017, Engelman 2009, Lindsley 2010, Liu et al 2009, Vanhaesebroeck et al 2012). They are activated in a wide range of solid and haematological malignancies. In breast cancer, AKT pathway activation is largely due to input from signals upstream of AKT, including activating mutations in the catalytic subunit of PI3K (PIK3CA) or deleterious mutations in PTEN, or through non-genomic mechanisms such as downregulation of PTEN protein expression or enhanced activation of receptor tyrosine kinases (Shi et al 2022, Yi and Lauring 2016).

There is evidence of a reciprocal activation between the ER pathway and the PI3K AKT pathway which can influence therapeutic response to each monotherapy agent. AKT signalling may be upregulated following exposure to ER inhibitors independent of genetic alterations, and the therapeutic benefit of inhibiting PI3K-AKT signalling may be limited through increased ER signalling (Bosch et al 2015, Miller et al 2010, Ribas et al 2015).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The diagnosis of breast cancer is based on clinical examination in combination with imaging and confirmed by pathological assessment. Disease stage is assessed according to the tumour, node, metastasis (TNM) system.

Recent ASCO/College of American Pathologists guidelines still support the classification of ER+ breast cancer being >1% by immunohistochemistry staining. However, "there are limited data on endocrine therapy benefit for cancers with 1% to 10% of cells staining ER positive. Samples with these results should be reported using a new reporting category, ER Low Positive".

Other therapeutically relevant biomarkers that may be evaluated in patients with ER+, HER2- mBC currently include PIK3CA, ESR1, NTRK, MSI-H/dMMR, TMB-H, RET, BRCA1/2 and PALB2.

Key clinical factors to consider when determining the choice for systemic treatment for women are (i) pre- versus postmenopausal status at the time of presentation, (ii) de novo metastatic versus recurrence, (iii) disease-free interval and type of adjuvant therapy, (iv) tumour burden including bone-only versus visceral disease, (v) performance status and medical comorbidities, and (vi) for patients who have

progressed on frontline treatment to consider the previous treatments they received and the response, duration of response, and tolerability to those previous therapies (Andrew et al, *JCO Oncology Practice*, 2021).

2.1.5. Management

Advanced breast cancer comprises both locally advanced (inoperable) and metastatic breast cancer. It remains virtually incurable (Gennari et al 2021). The primary goals of systemic treatment for advanced breast cancer (aBC) are prolongation of survival, alleviation of symptoms, and maintenance or improvement in quality of life, while balancing the toxicity associated with treatment (UpToDate 2023).

The preferred treatment for advanced HR+, HER2– breast cancer is sequential endocrine-based therapy in the majority of cases, except for patients with visceral crisis / imminent organ failure or where there is concern about (or evidence of) endocrine therapy resistance. For these patients, chemotherapy is the preferred option (NCCN 4.2023; Gennari et al, Annals of Oncology, 2021).

The combination of endocrine therapy (i.e. aromatase inhibitor or fulvestrant) with a CDK4/6 inhibitor (i.e. albemaciclib, ribociclib or abemaciclib) is currently considered the standard of care first-line treatment for advanced disease in the majority of patients, with improved PFS and OS seen in several trials (Gennari et al 2021, Hortobagyi et al 2021, Im et al 2019, Slamon et al 2020, Sledge et al 2020). Regarding the choice of using aromatase inhibitor or fulvestrant as endocrine therapy, the following applies:

- For patients who did not relapse on an aromatase inhibitor, or within 12 months of stopping adjuvant aromatase inhibitor therapy, a CDK4/6 inhibitor is generally deployed in combination with an aromatase inhibitor.
- In patients who relapsed on adjuvant aromatase inhibitor therapy, or within 12 months of stopping adjuvant aromatase inhibitor therapy, fulvestrant is advised as a combination partner with the CDK4/6 inhibitor (Gennari et al 2021).

The optimal sequence of endocrine-based therapy after progression on CDK4/6 inhibitors is uncertain and limited data is available in the post-CDK4/6 inhibitor setting. It is dependent on disease burden, which agents were used previously [in the (neo)adjuvant or advanced settings], duration of response (DoR) to previous ET (for use of second-line single-agent ET), patient preference and treatment availability. Subsequent available treatment options with some scientific evidence include (incomplete list) fulvestrant (+ CDK 4/6 inhibitor if not previously used), everolimus + endocrine therapy (exemestane), fulvestrant + alpelisib (if PIK3CA mutated tumours), elacestrant (if ESR1 mutated tumours) and chemotherapy. As a consequence, subsequent treatment with endocrine monotherapy, including fulvestrant, remains an option in current international guidelines (NCCN 2023), but is not the preferred option, as it has recently shown short PFS outcomes in CDK4/6 inhibitor pre-treated populations (Bidard et al 2022, Kalinsky et al 2022, Lindeman et al 2021, Tolaney et al 2022).

Premenopausal women must have ovarian suppression/ablation when treated with aromatase inhibitors.

This application for capivasertib is the first for an AKT-inhibitor. Several AKT-inhibitors are under development in different indications as the PI3K/AKT/PTEN pathway is a central signal transduction pathway in cell proliferation and survival. Other medicinal products targeting the PI3K/AKT/PTEN pathway target PIK3CA inhibitors and mTOR inhibitors (Coleman, 2021). The PIK3CA inhibitor alpelisib (in combination with fulvestrant) and the mTOR inhibitor everolimus (in combination with exemestane) are approved for advanced and metastatic breast cancer.

2.2. About the product

Capivasertib is a potent, selective inhibitor of the kinase activity of all 3 isoforms of serine/threonine kinase AKT (AKT1, AKT2 and AKT3). AKT is a pivotal node in the phosphatidylinositol 3-kinase (PI3K) signalling cascade regulating multiple cellular processes including cellular survival, proliferation, cell cycle, metabolism, gene transcription and cell migration. AKT activation in tumours is a result of upstream activation from other signalling pathways, mutations of *AKT1*, loss of p and tensin homolog (PTEN) function and mutations in the catalytic subunit of PI3K (*PIK3CA*).

The final indication for Truqap is:

'TRUQAP is indicated in combination with fulvestrant for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine-based regimen (see section 5.1).

In pre- or perimenopausal women, TRUQAP plus fulvestrant should be combined with a luteinising hormone releasing hormone (LHRH) agonist.

For men, administration of LHRH agonist according to current clinical practice standards should be considered.'

Treatment with TRUQAP should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Patients with ER-positive, HER2-negative advanced breast cancer should be selected for treatment with TRUQAP based on the presence of one or more *PIK3CA/AKT1/PTEN* -alterations which should be assessed by a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used.

Posology

The recommended dose of TRUQAP is 400 mg (two 200 mg tablets) twice daily, approximately 12 hours apart (total daily dose of 800 mg), for 4 days followed by 3 days off treatment. See Table 2.

Table 2 TRUQAP dosing schedule for each week

Day	**1**	**2**	**3**	**4**	**5***	**6***	**7***
Morning	2 x 200 mg	2 x 200 mg	2 x 200 mg	2 x 200 mg			
Evening	2 x 200 mg	2 x 200 mg	2 x 200 mg	2 x 200 mg			

* No dosing on day 5, 6 and 7.

TRUQAP should be coadministered with fulvestrant. The recommended dose of fulvestrant is 500 mg administered on Days 1, 15, and 29, and once monthly thereafter.

Missed dose

If a dose of TRUQAP is missed, it can be taken within 4 hours after the time it is usually taken. After more than 4 hours, the dose should be skipped. The next dose of TRUQAP should be taken at the usual time. There should be at least 8 hours between doses.

2.3. Type of application and aspects on development

This application under an article 8(3) legal basis of Directive 2001/83/EC (as a complete and independent application) is based on data from the primary analysis of PFS (DCO1) from the ongoing single pivotal

phase 3 study D3615C00001 (CAPItello-291), together with supportive data from other studies in the capivasertib (AZD5363) clinical development programme.

Specific CHMP guidelines relevant for the current application: Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev.5, 22 September 2017).

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 160 mg or 200 mg of capivasertib as active substance.

Other ingredients are:

Core tablet: microcrystalline cellulose (E460i), dibasic calcium phosphate, croscarmellose sodium (E468) and magnesium stearate (E470b).

Tablet coating: hypromellose, titanium dioxide (E171), macrogol 3350, polydextrose, copovidone, medium-chain triglycerides, black iron oxide (E172), red iron oxide (E172), yellow and iron oxide (E172).

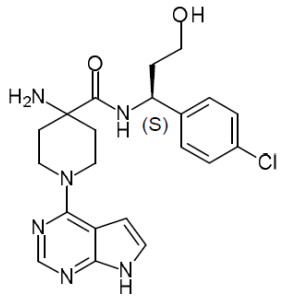
The product is available in aluminium/aluminium blister as described in section 6.5 of the SmPC.

2.4.2. Active Substance

General information

The chemical name of capivasertib is 4-amino-*N*-[(1*S*)-1-(4-chlorophenyl)-3-hydroxypropyl]-1-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidinecarboxamide corresponding to the molecular formula $C_{21}H_{25}ClN_6O_2$. It has a relative molecular mass of 428.92 g/mol and the following structure:

Figure 1: active substance structure



The chemical structure of capivasertib was elucidated by a combination of ^{1}H- and ^{13}C-NMR spectroscopy, mass spectrometry, infrared spectroscopy, UV spectroscopy and elemental analysis. Single crystal x-ray diffraction was used to confirm the absolute stereochemistry. The solid-state properties of the active substance were measured by thermogravimetric analysis, differential scanning calorimetry, and dynamic vapour sorption.

The active substance is a white to off-white non-hygroscopic crystalline solid exhibiting pH dependent solubility in biorelevant aqueous media with higher solubility at acidic pH. Particle size is controlled in the active substance specification. Several polymorphic forms were identified during development studies and the proposed commercial form is thermodynamically stable with respect to the others.

Manufacture, characterisation and process control

Capivasertib is synthesised by a single manufacturer in a convergent process using well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. he specifications and control methods for intermediate products, starting materials and reagents have been presented and are considered adequate.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Fate and purge studies informed and justified the limits for impurities in specifications.

The active substance is packaged in a container that complies with Commission Regulation (EU) 10/2011, as amended.

Specification

The active substance specification includes tests for description (visual), identity (FT-IR), assay (LC), impurities (LC), chiral impurity (chiral LC), residual solvents (HS-GC), water content (KF), and particle size distribution (laser diffraction).

The specification for the active substance capivasertib contains all relevant parameter to sufficiently describe, qualify and quantify the active substance and potential impurities. The range for assay and the limits for individual impurities are in accordance with ICH Q3A.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Stability

Stability data from batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (25ºC / 60% RH), for up to 24 months under intermediate conditions (30 ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: description, assay, impurities, chiral impurity, water content, particle size distribution and polymorphic form. The analytical methods used were the same as for release and were stability indicating. Batches were also tested annually for microbiological activity and water activity using appropriate methods. All tested parameters were within specification at all timepoints under all conditions and no trends were observed.

Photostability testing following the ICH guideline Q1B was performed showing that capivasertib is photostable. The active substance is also stable to thermal stress.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months in the proposed container. The applicant has chosen to include a temperature restriction of not more than 30ºC.

2.4.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Capivasertib 160 mg tablets are presented as beige, round, biconvex, film-coated tablets, approximately 10 mm in diameter. The tablets are marked with 'CAV' above '160' on one side and plain on the reverse.

Capivasertib 200 mg tablets are presented as beige, capsule-shaped, biconvex, film-coated tablets, approximately 14.5 x 7.25 mm. The tablets are marked with 'CAV200' on one side and plain on the reverse.

The tablets are sufficiently distinguishable by size, shape and imprinting.

The function of each component and a reference to their quality standards is indicated. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

The aim of development was an immediate release solid oral dosage form containing the requisite active substance content. Capivasertib is a BCS class IV compound (low solubility, low permeability). Studies demonstrated that particle size has little impact on dissolution, finished product formulation, and the resultant tablet attributes within the ranges studied. Particle size is limited in line with active substance used in these studies. The proposed specification criterion is clinically relevant and confirms acceptable product performance.

Bridging between formulations was demonstrated in a clinical bioequivalence study. Dissolution profiles in all tested media were considered equivalent.

During the development of the manufacturing process, manufacturing steps were evaluated on their potential impact on the quality attributes of the finished product (description, uniformity of dosage units, dissolution) based on failure mode risk analysis. The proven acceptable ranges (PARs) for the process parameters were taken from these development studies.

Systemic development of the dissolution method was discussed. *In vitro in vivo* correlation data assisted in the selection of the dissolution method and acceptance criteria. The proposed method is considered sufficiently discriminatory and is adequate for quality control purposes.

The primary packaging is aluminium/aluminium blisters. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by a standard process. PARs, NORs and target set-points have been assigned to relevant process parameters based on the development studies, as requested by the CHMP during the procedure. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Formal validation will be conducted on 3 consecutive production scale batches of finished product post-approval. A validation protocol has been submitted which is considered acceptable.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including description (visual inspection), identification (NIR, LC/UV), assay (NIR, LC), degradation products (LC), dissolution UV) and uniformity of dosage units (Ph. Eur.).

The specifications and associated limits are set in line with ICH and EU guidance. The absence of tests for chiral purity, microbiological attributes and water content has been adequately justified.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Analysis data 3 batches of each strength using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, no elemental impurity controls are included in the finished product specification.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The product is indicated for advanced cancer in line with ICH S9, and thus, ICH Q3B limits for nitrosamine impurities would apply. It has been justified that there is no appreciable risk of generating nitrosamine impurities at in relevant amounts.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 pilot scale batches of 160 mg tablets and 3 production scale batches of 200 mg tablets, stored for up to 36 months under long term conditions (25ºC / 60% RH), for up to 36 months under intermediates conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for description, assay, degradants, chiral impurity, dissolution, water content, hardness, microbiological activity and water activity. The analytical methods used in stability studies which are different from those already described in the specification section (assay and degradation products by LC, chiral impurity, water content) are provided with their corresponding validation data and are considered acceptable. No meaningful changes to any of the measured parameters and no trends were observed.

Photostability testing was carried out according to the conditions defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is photostable.

Based on available stability data, the proposed shelf-life of 48 months without specific storage conditions as stated in the SmPC (section 6.3 and 6.4) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Capivasertib has been evaluated in a comprehensive non-clinical package of in vitro and in vivo studies that were designed to characterise its pharmacology, safety pharmacology, pharmacokinetics and toxicity.

Non-clinical studies relevant for the non-clinical safety assessment of capivasertib (pivotal safety pharmacology studies, pivotal repeat-dose toxicology studies, embryo-foetal development study in rats, validation of bioanalytical methods, rat quantitative whole-body autoradiography (QWBA) study and rat mass balance study) were conducted in compliance with good laboratory practice (GLP) principles.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro activity

The potency and selectivity of capivasertib as a serine/threonine kinase AKT (AKT1, AKT2 and AKT3) inhibitor were determined by biochemical assays using isolated enzyme complexes. Capivasertib showed a strong inhibition of all AKT isoforms: AKT1, AKT2 and AKT3 with IC_{50} values of 3.2, 8.5 and 7.7 nM, respectively. Other kinase targets with the IC_{50} in low nanomolar range included PKA (IC_{50} = 6.6 nM) and p70S6K (IC_{50} was 5.8 nM in a radioactive filter binding assay and 8.9 nM in a recombinant kinase assay). ROCK1 and ROCK2 were also inhibited, albeit with a lower potency (IC_{50} was 126 and 56 nM, respectively). Screening in several kinase panels with up to 402 targets also identified interactions with MSK1/2, MKK1 (MEK1), RSK1/2/3, PKC, PrKX, PKG1α/β, CLK2, KIT, LATS2, and YSK4. Most of them belong to the AGC kinase family. The majority of capivasertib targets are involved in PI3K/AKT or MEK/ERK signalling. The latter may be beneficial as co-activation of the ERK pathway can modify response to PI3K and AKT inhibitors (Soares et al. 2015).

Capivasertib inhibited the activation of downstream targets of AKT, namely GSK3β, PRAS40 and S6, in various cancer cell lines with IC_{50} values in the range 0.07 - 2.57 µM. The effect on these AKT substrates was even more pronounced in LNCaP hormone sensitive PTEN null prostate cancer cells with IC_{50} between 0.08 and 0.36 µM. As ROCK inhibition may activate AKT through PTEN suppression (Yang and Kim 2014), it was important to evaluate the selectivity of capivasertib for AKT over ROCK. Indeed, capivasertib did not inhibit the phosphorylation of cofilin (S3), which is a downstream target of ROCK in MDA-MB-468 breast cancer cells (IC_{50} > 19.8 µM). IC_{50} for the inhibition of the phosphorylation of the PKA substrate VASP in different cell lines lay between 1.44 and 10.58 µM. Direct activity of capivasertib on p70S6K and its downstream substrate S6 was evaluated in TSC2 null and TCS2 knockout cells, in which AKT is no longer able to regulate mTORC1/p70S6K signalling. Capivasertib was less effective in inhibiting S6 phosphorylation in TCS2-deficient cells (IC_{50} around 800 nM) as compared to the wild-type cells (IC_{50} = 110 nM). Although most of these studies were based on Western blot analysis, which is a semi-quantitative technique, the results are consistent and the conclusions are agreed. Thus, beside the targets downstream of AKT, capivasertib also inhibits p70S6K and PKA but the potency in tumour cells is reduced compared to AKT target inhibition. In cellular assays and animal models, significantly increased phosphorylation of AKT by capivasertib rather than reduction in pAKT levels was observed.

Screening of anti-proliferative activity of capivasertib in a panel of 177 cell lines demonstrated the best results in breast cancer cells. There was a statistically significant correlation between sensitivity to capivasertib and mutations in the PIK3CA ($p = 0.03$) and PTEN ($p = 0.02$) among all cell lines examined. In the other two cell line panels, the activity was observed also in wild-type PIK3CA, AKT1 and PTEN cells, albeit less often than in cells with alterations in these genes: 44% of altered cell lines in a breast cancer cell line panel were responsive to capivasertib compared to 12% of WT cell lines, in another panel with different tumour types activity was noted in 67% of mutated lines and in 57% of WT cell lines. Lower IC50 was associated with PTEN altered breast cell lines ($p = 0.022$) but not in the cell panel of multiple cancer types. In palbociclib-naive and palbociclib-resistant ER+ PI3Kα mutant cell lines, the addition of capivasertib to fulvestrant or palbociclib increased efficacy compared to the single agent

treatments. Combination of capivasertib and fulvestrant was more effective than each agent alone in these cell lines also when tested in a long-term cell growth assay using a 4-day on/3-day off capivasertib treatment schedule similar to the clinical setting.

The major human metabolite AZ14102143, an ether glucuronide of capivasertib, did not affect the phosphorylation of PRAS40, S6 or GSK3β at the concentrations up to 10 μM and is thus considered a pharmacologically inactive metabolite.

In vivo activity

When administered orally once or twice daily capivasertib inhibited tumour growth in various mouse xenograft models in a dose-dependent manner. Tumour regression was observed in 786-0 PTEN null renal cancer xenografts (125% tumour growth inhibition at 150 mg/kg BID), in PIK3CA mutant/PTEN null HGC-27 gastric cancer xenografts (106% and 108% tumour growth inhibition at 100 and 150 mg/kg BID, respectively), and HCC-1954 breast cancer xenografts (111% and 129% tumour growth inhibition at 75 and 150 mg/kg BID, respectively). In xenograft models, capivasertib inhibited phosphorylation of PRAS40, GSK3β and S6 in a time- and dose-dependent manner, with 50% PRAS40 inhibition at plasma concentrations of capivasertib around 0.1 – 0.2 μM. This is well below the clinical unbound Cmax of 0.717 μM demonstrating pharmacological activity of capivasertib at clinically achievable plasma drug levels.

The impact of dosing schedule on capivasertib's efficacy was evaluated in BT474c breast cancer xenografts in mice but with different results. In one study, a high intermittent dose (300 mg/kg once daily 4 days on/3 days off) achieved regression with tumour regrowth during the OFF period whereas the highest continuous dose (150 mg/kg BID) only led to tumour growth inhibition and tumour stasis, despite the higher overall drug load upon continuous schedule (1200 mg/kg/week and 2100 mg/kg/week, respectively). In another study in the same xenograft model, tumour growth inhibition at 300 mg/kg QD 4 on/3 off was inferior to the continuous 150 mg/kg BID dosing. Multiple experiments were performed to mitigate the influence of experiment to experiment variation. Across the whole data set multiple dose schedules (QD and BID, different intermittent dosing schedules) were compared, and conclusions based on modelling of the total data set.

In patient-derived ER+ breast cancer xenografts, capivasertib in combination with fulvestrant elicited a dose-dependent tumour inhibition response, which was superior to the single agent fulvestrant. This was accompanied by an increase in pAKT levels and a reduction in pPRAS40 and pS6 at different dose levels dependent on the model.

In a model of tumour with primary endocrine resistance, continuous administration of 50 mg/kg capivasertib twice daily resulted in a significant reduction in tumour growth compared to vehicle control. Combination with fulvestrant further improved the outcome significantly (to 80% tumour growth inhibition) compared to capivasertib and fulvestrant monotherapy.

In a panel of ER+ breast cancer in vivo models including palbociclib-sensitive and palbociclib-resistant models as well as PI3KCA, AKT1 and PTEN altered and unaltered models, the combination of capivasertib and fulvestrant showed improved activity compared to each agent alone. The combination benefit was seen in PI3KCA, AKT1 and PTEN mutated and also tumours without alterations, although generally better activity on the combination was noted in altered models.

2.5.2.2. Secondary pharmacodynamic studies

Table 3 Effect of capivasertib in in vitro radioligand binding, enzyme, and electrophysiological assays

Target [a]	IC_{50} (µmol/L)	Ki (µmol/L)	slope
ROCK1, Protein Serine/Threonine Kinase	0.47	n.d.	n.d.
FGFR1, Protein tyrosine Kinase	6.06	n.d.	n.d.
Melanocortin MC5	7.77	7.29	0.933
YES1, Protein Tyrosine Kinase	11.1	n.d.	n.d.
UGT1A1, UDP Glucuronosyltransferase	12.8	n.d.	n.d.
PDE4, Phosphodiesterase	37.5	n.d.	n.d.
Calcium channel L-type, Benzothiazepine (Rat)	40.8	36.2	0.963
Proteasome	62.3	n.d.	n.d.

[a] All human except where noted

n.d = Not determined

In a panel of 333 in vitro radioligand binding and enzyme assays consisting of various receptors, enzymes and ion channels, significant activity with IC50 values between 6.06 and 62.3 µM was detected for 7 targets including PDE4, FGFR1, Melanocortin MC5, UGT1A1, Proteasome, Calcium Channel L-type benzothiazepine Receptor and YES1. These IC50 values are more than 8.4-fold higher than the unbound clinical Cmax of 0.717 µM. Therefore, the interactions with these targets are not considered clinically relevant. In the secondary pharmacology screening, ROCK1 was also identified as a potential target with the IC50 value of 0.47 µM. This concentration is within the clinical range but capivasertib had no effect on the downstream targets of ROCK, therefore, its interaction with ROCK is not considered clinically relevant (see also section 2.5.2.1. In an electrophysiological assay, capivasertib inhibited voltage-gated cardiac ion channels hCav3.2 and hNav1.5 by 25.5% and 29.6%, respectively, at 100 µM.

2.5.2.3. Safety pharmacology programme

In vivo and *in vitro* safety pharmacology studies were performed to assess the cardiac safety, respiratory effects, and neurological effects of capivasertib. Other safety pharmacology studies investigated the effects of capivasertib on the gastrointestinal system and the urinary system.

Cardiovascular System

GLP study 0354SZ used the patch clamp technique to investigate the effects of capivasertib on the voltage-dependent potassium channel encoded by the human ether-a-go-go-related gene (*hERG*), which was expressed in Chinese Hamster Ovary (CHO) cells. Capivasertib exerted concentration-dependent hERG channel activity with the IC_{50} value of 73.0 µM. This is more than 100-fold of the unbound clinical Cmax.

In GLP study 1101ZD, the effects of single oral administration of 5, 30 and 40 mg/kg capivasertib to male beagle dogs on arterial blood pressure, left ventricular (LV) systolic and end diastolic pressure, LVdp/dt+ (an index of myocardial contractility), LVdp/dt- (an index of myocardial relaxation), heart rate and ECG parameters (PR, QRS and QT) were recorded by telemetry. Capivasertib at 5 mg/kg decreased heart rate by 17 and 14% at 2 and 8 h, respectively. Following administration of 30 and 40 mg/kg capivasertib, there were peak decreases in systolic and diastolic blood pressure of 20 to 25% and 28 to 30%, respectively, which reversed at 4 h. Heart rate decreased at all doses but the reduction was

reversible. 30 and 40 mg/kg capivasertib caused a sustained statistically significant prolongation of the QT interval (6 to 13%) and QTcR (5 to 12%). There were sustained increases in LVdp/dt+ with peaks of 45 and 56% at 6 and 8 hours. Both glucose and insulin levels were elevated post 30 and 40 mg/kg dose. The NOAEL was considered to be 5 mg/kg. The total Cmax in dogs at the NOAEL was 1.45 µM, which corresponds to unbound Cmax of 0.28 µM, being below the expected clinical exposure.

GLP study 1167ZD aimed to evaluate the effects of oral administration of 30 mg/kg capivasertib (three dosing occasions) to conscious male beagle dogs on arterial blood pressure, heart rate, left ventricular parameters, lead II electrocardiogram (ECG), body temperature and to see whether the effects on myocardial contractility could be reduced by the intravenous administration of either atenolol or verapamil. Capivasertib resulted in an increase in left ventricular (LV) dp/dtmax of 34 - 65%. QT and QTcR were both prolonged by 4 - 16% and 5 - 11%, respectively. Intravenous infusion of atenolol significantly reduced LVdp/dtmax by 17% compared to the time-matched vehicle data. LVdp/dtmax returned to the baseline levels 4 h post-infusion compared to the vehicle control where contractility had not recovered until 8 h post-infusion. IV administration of verapamil decreased LVdp/dtmax by a maximum of 18%. Increases in glucose (2.5- to 2.8-fold) and insulin (129- to 170-fold) levels were observed at 4 h after administration of capivasertib. Atenolol and verapamil significantly reduced glucose increases (1.2- and 1.5-fold increase, respectively) compared to vehicle (2.6-fold increase). Insulin level increase was also reduced by atenolol (27-fold increase) and to a lesser extent by verapamil (47-fold increase), compared to vehicle (140-fold increase).

Study 2192SV tested the effects of capivasertib on action potential parameters in dog ventricular myocytes. Although capivasertib exerted biphasic effects on action potential duration (APD), these effects were not statistically significant. At lower concentrations (0.3 - 30 µM), there was an increase in APD90 (16.93% at 30 µM), while at a higher concentration of 100 µM a decrease in APD90 of 5.18% seen. Similar biphasic effects were found for APD70 and APD50.

Study 0255SB tested capivasertib's effect on ventricular monophasic action potentials recorded in Langendorff heart model from female New Zealand white rabbits. Capivasertib caused a reduction in the APD at 60% of repolarisation (APD60) with a "bell-shaped" concentration-effect curve. A concentration-related increase in coronary blood flow was noted. There was a low-frequency incidence of the indicators of proarrhythmic risk (triangulation, reverse-use dependence or instability) but no early after-depolarisations. At some capivasertib concentrations greater than 1 µM, ventricular tachycardia was seen in 50% of hearts; the reasons behind this effect remain unclear as any effects on conduction were absent. Up to 30 µM, the TdP proarrhythmic score was less than 25 (the threshold for concern defined by Lawrence et al. 2006).

Study 2820SR tested capivasertib's effects on coronary flow, heart rate and cardiac contractility in isolated rat hearts perfused in the Langendorff model. At 3, 10 and 30 µM, capivasertib resulted in a significant dose-related but reversible increase in coronary flow (respectively +34.7%, +80% and +101.7% compared to baseline). No statistically significant effects on cardiac contractility were noted up to 10 µM. At 30 µM, a small increase of differential left ventricular pressure (+14%, $p=0.051$), no effect on mean left ventricular pressure, a small increase of dP/dt min (+10%, $p<0.001$) and dP/dt max (+13%, $p<0.001$) were observed but these effects were reversible. No statistically significant effects on heart rate were noted. Verapamil at the concentration of 1 µM attenuated the observed effects.

Study PH/E/12009 assessed the impact of capivasertib on rat aortae. The compound induced direct relaxation of pre-constricted rat aortae, with a minimally active concentration between 1 and 3 µM and significant relaxation at 30 µM and above.

Study 0159SG evaluated the effects of capivasertib on ventricular monophasic action potentials and the surface electrocardiogram in male anaesthetised guinea-pigs, which received either two consecutive infusions of vehicle, or two consecutive infusions of capivasertib at the dose 3.5, 35 or 17.5 mg/kg,

respectively. Capivasertib given at 3.5 mg/kg produced no treatment-related effects. Administration of 35 mg/kg capivasertib caused the death of two animals. Prior to death, a pronounced reduction in blood pressure (44%) and heart rate (27%) were recorded and significant ECG waveform changes were seen, indicating a marked ischaemic insult. A trend (31%) towards an increase in AV conduction time was noted towards the end of the 35 mg/kg infusion. The dose was lowered to 17.5 mg/kg and the remaining animals survived. Maximum total plasma concentrations of capivasertib were 7.36, 42.90 and 90.01 μM during administration of 3.5, 17.5 and 35 mg/kg, respectively.

Study0209SG assessed the effects of capivasertib on arterial blood pressure, heart rate, electrocardiogram (ECG) and left ventricular parameters in male anaesthetised guinea-pigs, which received a single intravenous infusion of either 10 or 3.33 mg/kg capivasertib. Capivasertib administered at 3.33 and 10 mg/kg led to reductions in blood pressure by 16 and 38%, in heart rate by 10 and 24%, left ventricular systolic pressure by 19 and 30% and contractility by 41 and 47%, respectively. No increase in contractility as was seen in dogs in study 1101ZD was observed in guinea-pigs. A rise in glucose levels was noted at both dose levels.

Study 3316SR determined the suitability of changes in rat QA interval as a predictor of left ventricular dP/dt changes observed in dogs after capivasertib treatment. Rats received oral doses of 25, 75, and 150 mg/kg of capivasertib in a cross-over design. Capivasertib decreased heart rate by 21% after the 25 mg/kg dose and decreased arterial pressure 19 to 30 % after both 75 and 150 mg/kg doses without any further significant changes in heart rate. Capivasertib produced non-significant decreases in QA interval, indicative of increased cardiac contractility. Thus, changes in QA interval cannot be used as a surrogate for increases in cardiac contractility. Biologically and statistically significant reductions in blood pressure were found after administration of the 75 mg/kg dose. The 25 mg/kg dose was considered the NOAEL since the associated heart rate reductions were not seen as biologically significant.

The effects of 150 mg/kg p.o. capivasertib on cardiovascular parameters were assessed in conscious, unrestrained rats implanted with a radio telemetry device in study PH/E/13611. Transient, mild changes in blood pressure and heart rate were noted but these findings appeared coincidental to increased animal activity and were not thought to be due to pharmacology. One rat was found dead several hours after dosing, but due to experience in other rat studies and the lack of any previous adverse signs in the animal, the finding was considered not related to the test compound.

Cardiovascular effects (QTc interval prolongation, increased cardiac contractility, and decreased blood pressure) were seen in dogs at plasma concentrations approximately 1.4 to 2.7 times the expected clinical exposure in humans at the recommended dose of 400 mg twice daily (based on unbound Cmax).

Central nervous & respiratory systems

As part of GLP study 2692SR, the effects of capivasertib in the rat on the nervous system (using a modified Irwin screen), on the respiratory system using whole body plethysmography and on gastric emptying and intestinal transit using a charcoal meal were studied. Rats were treated with vehicle or capivasertib at the dose levels of 30, 100 or 150 mg/kg by oral gavage. In the modified Irwin screen, decreased spontaneous activity and decreased touch response was noted in the 100 and 150 mg/kg groups. The NOEL was considered to be 30 mg/kg. At this dose level, the rat unbound Cmax was 0.65 μM, which is in the range of the expected clinical Cmax. Body weight was decreased in the 100 and 150 mg/kg groups. There were no effects on respiratory parameters at any dose level tested. Capivasertib caused a statistically significant inhibition of gastric emptying at 100 and 150 mg/kg, with increases in stomach contents of 168% and 192% compared to vehicle. This was accompanied by decreases in intestinal transit, with a statistically significant reduction of 41% at 150 mg/kg. Animals had group mean exposures of 0.624, 4.03 and 4.28 μM capivasertib in the Irwin arm of the study, or 0.946, 3.32 and 7.08 μM in the respiratory arm of the study, or 2.33, 6.09 and 6.06 μM in the charcoal meal arm of the study (following 30, 100 or 150 mg/kg capivasertib, respectively). In the modified Irwin screen and in

the charcoal meal arm of the study, a NOEL of 30 mg/kg capivasertib was identified. A NOEL of at least 150 mg/kg capivasertib was set in the respiratory arm. The unbound animal Cmax at the NOEL was 3.8 µM, which is 5.3-fold higher than the expected human exposure.

Other organ systems

GLP study 09-6713 examined the effects of vehicle and 30, 100 or 150 mg/kg oral capivasertib on urine and electrolyte excretion in male Han Wistar rats. Capivasertib administration led to a marked glucosuria at ≥100 mg/kg with concurrent diuresis. Increases in fractional excretion were seen at all doses for sodium and chloride, and at ≥100 mg/kg for potassium and phosphorus. In addition, albumin concentration was marginally increased at ≥100 mg/kg. Decrease in plasma potassium and increases in plasma phosphorous and urea nitrogen were seen at ≥100 mg/kg. It was thus not possible to determine a NOEL.

2.5.2.4. Pharmacodynamic drug interactions

No drug interaction study was conducted in animals (see section 2.5.6. .

2.5.3. Pharmacokinetics

The absorption, distribution, metabolism and excretion of capivasertib has been studied in the mouse, rat and dog in vivo and in mouse, rat, dog and human tissues and biomaterials in vitro. In vitro studies were conducted to determine plasma protein binding, blood-plasma partitioning, cross-species metabolism including the enzymes involved, interactions with cytochrome P450 (CYP) and uridine 5'-diphospho glucuronosyl transferase (UGT) enzymes, and interactions with transporter proteins. Absorption was evaluated within the toxicokinetic (TK) monitoring of the 1, 6 and 9-month repeat dose toxicity studies (see section 2.5.4.

Absorption

Study BE000747-32 investigated intestinal permeability of 250 µM capivasertib in the Ussing chamber using excised intestinal segments from human jejunum. The average permeability of capivasertib in this study was 4.3 x 10-6 cm/s indicating a low to moderate fraction absorbed in vivo in humans. The permeability of [14C]-capivasertib yielded a higher Papp value of 6.9 x 10-6 cm/s. This difference may be explained by metabolism in the intestinal tissue, an apparent extraction ratio of 38% indicates that approximately 40% of the compound is lost (metabolised) during the transport over the gut membrane.

The in vitro permeability assay utilising intestinal segments from human jejunum indicated that capivasertib is likely to have a low to moderate fraction absorbed in vivo in humans and that approximately 40% of the drug is likely to be metabolised upon transfer over the gut membrane.

No dedicated pharmacokinetic studies to evaluate the absorption of capivasertib were conducted. The absorption of capivasertib in vivo was investigated within the toxicokinetic evaluation in the toxicology studies (see section 2.5.4). Several pharmacodynamic and all pivotal in vivo safety pharmacology studies included pharmacokinetic evaluation (see section 2.5.2.

Distribution

In vitro study KPJ011 investigated the extent of binding of [14C]-capivasertib to human serum albumin, human alpha 1-acid glycoprotein, and to proteins in freshly prepared whole human (male and female) plasma and in frozen plasma of mouse (male), rat (male), dog (male) and human (male) in the concentration range 0.5 – 20 µg/mL (for mouse, rat and dog) and 0.05 - 5.0 µg/mL (for human plasma, serum albumin and α1-acid glycoprotein). Equilibrium dialysis method was utilised for this purpose. The

plasma/blood cell partitioning of the radioactive capivasertib in male human blood at a concentration of 0.5 µg/mL was evaluated after incubation for 120 minutes. The non-specific binding of [^{14}C]-capivasertib to the equilibrium dialysis apparatus was found to be approximately 8%, which was still considered acceptable by the applicant. The overall mean extent of plasma protein binding of [^{14}C]-capivasertib decreased in the following order: mouse 83.3% to 85.7% > dog 77.1% to 80.8% > rat 74.9% to 76.5%. Plasma protein binding in human was similar to dog: fresh male human plasma 78.1% to 78.9%, frozen male human plasma 77.1% to 77.9%, fresh female human plasma 76.8% to 77.5%. The mean unbound fraction in human plasma was determined as 22.3%. The extent of protein binding to human serum albumin was in the range 70.0% to 71.3%, binding to alpha 1-acid glycoprotein was lower (24.2% to 33.5%). Therefore, albumin is likely the major human binding protein in vivo. The mean plasma : blood ratio of radioactivity concentration was 0.714 and the mean proportion of [^{14}C]-capivasertib associated with blood cells in vitro was 61%.

Study BS003919-61 investigated human plasma protein binding of major human metabolite AZ14102143 at the concentration of 5 µM after 18 h incubation using equilibrium dialysis. The free fraction was found to be 0.368±0.0292.

In study BS002913-71, equilibrium dialysis method was used to characterise protein binding of capivasertib in human liver microsomes after 4 h incubation. The unbound fraction was determined as 0.622±0.031.

Study BS003400-59 assessed protein binding of capivasertib at the concentration of 1 µM in human hepatocytes incubated with the compound for 4 h using equilibrium dialysis. The unbound fraction was calculated as 0.647 ± 0.019.

Study KMR012 investigated the time-dependent tissue distribution in rats after single oral administration of 10 mg/kg [14C]-capivasertib to male Lister Hooded and to male and female Han Wistar rats using a quantitative whole-body autoradiography. Total radioactivity was rapidly absorbed from the gastrointestinal tract and first widely distributed throughout the animal body. In pigmented rats, the highest concentrations were generally associated with the bile, liver, kidney, caecum wall, small intestine wall, urinary bladder and uveal tract of the eye remaining in the latter at least until 504 hours. Beside this apparent association with the melanin, there was no notable persistence of radioactivity in tissues. In male and female albino rats, the highest concentrations were generally associated with the bile, kidney, liver, small intestine wall, adrenal gland, oesophagus, pituitary and caecum wall.

Plasma protein binding of [^{14}C]-capivasertib decreased in the following order: mouse (83.3-85.7%) > human (76.8-78.9%) ≈ dog (77.1-80.8%) > rat (74.9-76.5%). The mean unbound fraction in human plasma was determined as 22.3%. In human plasma, serum albumin is a major binding partner (the extent of binding 70.0-73.1%). The free fraction of major human metabolite AZ14102143 in human plasma was determined as 0.368±0.0292. The mean plasma : blood ratio was 0.714 and the mean proportion of [^{14}C]-capivasertib associated with blood cells in vitro was 61%. The unbound fraction of capivasertib in human liver microsomes and in human hepatocytes was 0.622±0.031 and 0.647 ± 0.019, respectively. However, high stability and high recovery determined in those studies point at low non-specific binding.

Following single oral administration of 10 mg/kg [^{14}C]-capivasertib to male Lister Hooded rats, the highest concentrations were found in bile, liver, kidney, caecum wall, small intestine wall, urinary bladder and uveal tract of the eye, the latter suggesting association with melanin. In male and female Han Wistar rats, the highest concentrations were generally associated with bile, kidney, liver, small intestine wall, adrenal gland, oesophagus, pituitary and caecum wall.

Metabolism

In vitro metabolism

Study KMN010 assessed the in vitro metabolism of [14C]-capivasertib in fresh rat, dog and human hepatocytes as well as in cryopreserved human hepatocytes at the concentration of 10 µM. Metabolism of [14C]-capivasertib was most rapid in rat and dog hepatocytes (58.6% and 62.3% remaining, respectively) and slower in human hepatocytes (77.7 – 78.8% remaining). The major metabolite in dog and human was a glucuronide conjugate of [14C]-capivasertib. The major metabolite in the rat was a sulfate conjugate of [14C]-capivasertib. In addition, six mono-oxygenated metabolites were identified, as well as a hydrated, mono-oxygenated metabolite. Glucuronide and sulfate conjugates of monooxygenated metabolites were also observed. No human-specific metabolites were observed.

Study BS002337-76 estimated the contribution of phase 1 and phase 2 enzymes to the in vitro metabolism of capivasertib in human hepatocytes. The results revealed that capivasertib metabolic clearance is mediated approximately for 44% by phase 1 enzyme mechanisms (predominately oxidation), and for 53% by phase 2 enzymes (predominantly glucuronidation).

Study KMX013 investigated the metabolism of [14C]-capivasertib in human liver microsomes and with heterologously expressed human cytochrome P450 (CYP) and uridine 5'-diphospho glucuronosyl transferase (UGT) isoforms to identify the enzymes responsible for the drug metabolism. The formation of monooxygenated metabolites in human liver microsomes was inhibited in the presence of CYP3A4/5 and CYP2C9 antibodies (71-88% and 19-29% inhibition of metabolite formation, respectively). The experiments with heterologously expressed CYP isoforms confirmed that CYP3A4 was the major isoform involved in the formation of the metabolites, with a more minor contribution from CYP3A5 and CYP2C9 for some metabolites. In addition, some monooxygenated metabolites were produced by heterologously expressed CYP1A1. The major glucuronide conjugate of [14C]-capivasertib was observed after incubation with UGT1A9 and UGT2B7. A minor glucuronide metabolite was seen following incubation with UGT1A4.

Study BS002337-75 assessed the relative contribution of the major CYP isoforms to the metabolism of capivasertib through monitoring of substrate depletion in SilensomesTM, human liver microsomes where a specific CYP isoform is inhibited. Full abolishment of metabolic clearance in CYP3A4- SilensomesTM suggests that this isoform is primarily responsible for the CYP-mediated metabolism of capivasertib.

Study BS000901-99 aimed to estimate the relative contribution of each UGT isoform, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15, to the biotransformation of capivasertib using activated recombinantly expressed human UGTs. Capivasertib was found to be a substrate of UGT1A1, UGT1A3, UGT1A4, UGT1A9, and UGT2B7. The major human metabolite, an ether glucuronide, was formed by UGT2B7 contributing 84% and UGT1A9 with a contribution of 13%. UGT1A4 was the major enzyme involved in formation of a minor glucuronide contributing 100%. These data are in line with the results of study KMX013.

In vivo metabolism

Study YHM/003-4894KV aimed to profile and characterise the metabolites of [14C]-capivasertib in plasma, urine, faeces and bile following oral (10 mg/kg) administration to intact and bile duct cannulated (BDC) male and female rats, and intravenous (1 mg/kg) administration to BDC male and female rats. Parent capivasertib was identified as the major circulating drug-related component in intact rats and accounted for 63% of the plasma radioactivity AUC. In male rats, the most abundant metabolites were products of mono-oxidation on the piperidine ring (M17) and mono-oxidation on the pyrrolo-pyrimidine region of the molecule (M9). In female rats, the most abundant metabolite resulted from sulphate conjugation (M12). In intact rats, the largest proportion of the orally administered radioactive dose was excreted unchanged (33 and 49% of the dose in male and female animals, respectively), with the largest proportion being recovered in the faeces (28 and 46%) suggesting that oral absorption may not be complete. In the male animal faeces and bile, the most abundant metabolites were oxidation products. A sulphate conjugate M12 was the most abundant metabolite detected in the female excreta. It

accounted for 20% of the dose in the female animals and 1% in the male animals. The major human metabolite, glucuronide conjugate M11, was only detected in small quantities in BDC rats.

Metabolism of [^{14}C]-capivasertib was most rapid in rat and dog hepatocytes (58.6% and 62.3% remaining, respectively) and slower in human hepatocytes (77.7 – 78.8% remaining). The major metabolite in dog and human was an ether glucuronide conjugate of [^{14}C]-capivasertib. The major metabolite in the rat was a sulfate conjugate. In addition, oxidative metabolites and their glucuronide and sulfate conjugates were identified.

Capivasertib metabolic clearance is mediated approximately for 44% by phase 1 enzyme mechanisms (predominately oxidation), and for 53% by phase 2 enzymes (predominantly glucuronidation). The major human metabolite, an ether glucuronide, is formed predominantly by UGT2B7 with a minor contribution of UGT1A9. CYP3A4 is primarily responsible for the CYP-mediated metabolism of capivasertib. In addition, capivasertib is a substrate of UGT1A1, UGT1A3, UGT1A4 but their contribution to the overall metabolism of the compound is rather low.

In intact rats, unchanged capivasertib was the main component of the drug-related material in plasma and excreta. The major metabolites of capivasertib in male rats were oxidation products, whereas female rats mainly formed a sulfate conjugate. The major human metabolite, glucuronide AZ14102143, was only detected in bile duct-cannulated animals. No metabolism studies were performed in other species.

Excretion

GLP study KMR016 assessed the routes and rates of excretion of [14C]-capivasertib and its radioactive metabolites in urine and faeces of male and female Han Wistar rats following either a single oral (10 mg/kg) or intravenous (1 mg/kg) dose. Faecal recovery of radioactivity from intravenously dosed rats was lower than after oral administration (see below table.). Consequently, the mean recovery of administered radioactivity in urine following oral administration was lower than after intravenous administration. The ratio of blood: plasma radioactivity after oral administration suggested 35 to 45% blood cell binding. The total radioactivity concentrations in blood and plasma of female animals were generally lower than in male animals.

Study 182569-4330KR investigated excretion of [14C]-capivasertib following oral (10 mg/kg) and intravenous (1 mg/kg) administration to male and female bile-duct cannulated (BDC) Han Wistar rats. After oral dosing, biliary excretion was the predominant route of elimination. Urinary excretion was minor (8 – 13%). Given the levels of radioactivity in urine and bile, it can be estimated that 53 – 66% of the administered oral dose was absorbed. Following intravenous administration, biliary elimination was also the predominant route. The fraction of urinary elimination was higher than that of faecal excretion.

Table 4 Excretion routes of capivasertib in rats

Study ID	Dose (mg/kg)	Route	Species	N	Urine (% dose)	Faeces (% dose)	Bile (% dose)	Recovery (% dose)
KMR016	10	oral	HW rats M	3	3.48 ± 0.17	91.9 ± 0.55	n.a.	95.9 ± 0.57
	10	oral	HW rats F	3	2.69 ± 0.18	91.5 ± 2.24	n.a.	95.4 ± 1.91
	1	i.v.	HW rats M	3	16.8 ± 1.77	75.9 ± 3.28	n.a.	95.2 ± 5.14
	1	i.v.	HW rats F	3	15.3 ± 1.25	82.2 ± 1.09	n.a.	100 ± 0.56
4330KR	10	oral	BDC rats M	1	7.6	43.0	45.4	99.1
	10	oral	BDC rats F	2	12.9	32.6	53.0	99.9
	1	i.v.	BDC rats M	2	25.8	10.6	65.3	104.2
	1	i.v.	BDC rats F	2	24.0	13.4	63.5	104.7

In intact rats, capivasertib was predominantly excreted via faeces, with renal elimination contributing 3-17%. Following intravenous administration, the fraction of urinary excretion was higher than after oral dosing. In bile-duct cannulated rats, the proportion of biliary excretion was 45-65% indicating major elimination via bile. The fraction of renal elimination in bile-duct cannulated animals was higher compared to faecal excretion.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No stand-alone single dose toxicity studies have been performed.

2.5.4.2. Repeat dose toxicity

Rat

In the 1 month oral GLP-compliant toxicology study the potential toxicity and toxicokinetics of capivasertib in Han Wistar rats were evaluated after daily oral dose levels of 0, 10, 30 or 100 mg/kg. A one-month recovery period was included. Males had generally higher exposure levels than females (~2-fold AUC), except at 10 mg/kg on Day 1. Capivasertib-related effects occurred at the highest dose tested (100 mg/kg/day) and included changes in body weight (weight loss), food consumption (reduced), increase in water consumption, haematology (reduced lymphocyte and white blood cell counts in males), serum chemistry (elevated enzymes: AST, alkaline phosphatase (ALP), glutamate dehydrogenase (GLDH)), higher urine volume, macroscopic and microscopic observations in liver, pancreas, thymus, pituitary gland, adrenals, and reproductive system of males. The only changes of note at the end of the off-dose recovery period were reductions in the weight of the testes (26%) and epididymides (18%).

In the one month study, there were sex differences in exposure (based on AUC(0-last)) to capivasertib with greater plasma levels in males than females. Measurement of insulin in female animals and measurement of HbA1C levels were not assessed in either sex since data are available from the chronic six month rat study conducted at equivalent or higher doses.

In the 6-month oral GLP-compliant toxicology study, the potential toxicity and toxicokinetics of capivasertib in Han Wistar rats were evaluated when administered by daily oral administration at dose levels of 0, 10, 30, 100 (males only) or 150 mg/kg/day (females only). Capivasertib exposures, Cmax and AUC increased in a broadly dose-proportional manner across the respective dose range in males and females, although a high variation in AUC was observed at 30 mg/kg/day in females. Because of the inclusion of only 3 animals per dose, these data might reflect an inter-animal variation. At 100 mg/kg (males) and 150 mg/kg (females), clinical signs consisted of body weight loss, food reduction, increase in water consumption, haematology (reduced WBC, males only), serum chemistry (elevated AST, lower total protein), higher urine volume, macroscopic and microscopic observations in kidney, liver, endocrine pancreas, adrenal gland, thyroid gland, pituitary gland (males only), bone marrow and thymus, and reproductive system of males (testis and epididymis).

Dog

The objective of the GLP-compliant 28-day toxicity study was to evaluate the potential toxicity of capivasertib when administered orally by gavage at doses of 0, 3, 10 and 30 mg/kg once daily to Beagle dogs. The study included a one month recovery period. On days 1 and 28, capivasertib exposure in terms of mean Cmax and AUC(0-last) increased slightly more than in proportion to the dose of capivasertib in the dose range of 3 to 10 mg/kg (3.6- to 4.8-fold for a 3.3-fold increase in dose). No gender differences

were noted. Capivasertib-related changes at 30 mg/kg/day included body weight loss, reduced food consumption, changes in haematology (increase in platelet numbers), serum chemistry (minor increase in potassium in males and minor increase in ALP in females), decrease in urine specific gravity, macroscopic and microscopic observations in testes, epididymis, prostate, thyroid gland, adrenal gland, pancreas, liver and thymus.

Lesions in the prostate, thyroid gland, pancreas, liver and thymus were not present at the end of the recovery period in contrast to the changes observed in testes and epididymis, which were still present at the end of the recovery period.

Capivasertib induced a reduction of systolic left ventricular diameter, an increase of ejection and shortening fractions and a moderate decrease of cardiac output after dosing at 10 and 30 mg/kg/day. The effects were more pronounced in Week 1 than in Week 4 and were reversed at the end of the recovery period.

In the 9-months GLP-compliant oral toxicology study, capivasertib was administered by oral gavage at 0, 1.5, 5.0 and 15 mg/kg/day. Systemic exposure increased in a generally dose-proportional manner between 1.5 and 15 mg/kg/day; however, even at the maximum feasible dose of 15 mg/kg/day, exposures did not reach the levels as observed in the 6 month rat study. All in all, only a small margin of exposure (Rat: Males: 1.44, Females: 1.22; Dog: Males: 1.02, Females: 0.78) could be detected in these studies, especially with respect to the increased glycosylated haemoglobin and pathological changes in the male reproductive organs. No sex-related differences and no differences in Tmax or T1/2 of capivasertib across the dose range were noted. Capivasertib-related changes at 15 mg/kg/day included microscopic changes in the testis and epididymis, organ weight changes in testis (lower), epididymis (lower), liver (higher) and adrenal gland (higher). Vacuolation of the Langerhans islets of the pancreas occurred already at a dose of ≥5 mg/kg/day. Liver lesions were present in both rats and dogs with accompanying changes in liver enzymes. Findings in the liver were also present in the short-term studies in rats and dogs. These changes were not present at the end of the recovery period in both species in the 1 month rat and 1 month dog study and no abnormalities were observed in patients.

2.5.4.3. Genotoxicity

Genotoxicity testing of capivasertib was carried out in two in vitro (gene mutation tests in bacteria, mammalian chromosome aberration test) studies and three in vivo (two rat chromosome aberration / micronuclei tests including a kinetochore labelling of micronucleated polychromatic erythrocytes (PCEs), Comet assay) studies in compliance with GLP. In the in vivo studies, capivasertib was orally administered, which coincides with the intended clinical route. Dose selection was based on the maximum tolerated dose (MTD) determined in repeat-dose toxicity studies up to 6 months of treatment. No toxicokinetic (TK) data was determined in the in vivo studies but extrapolation from TK data obtained from repeat-dose toxicity studies in rats revealed a margin of exposure of approximately 1 at MTD (150 mg/kg) compared to the clinical exposure. Only male rats were used since no sex differences concerning toxicity and TK were observed in the repeat-dose toxicity studies.

In vitro

For the detection of gene mutations in bacteria, an AMES test (study 2332BV) was conducted. Independent of precipitation or cytotoxicity observed at high concentrations, capivasertib was negative for relevant increase in reverse mutations with and without metabolic activation in all tester strains up to the top concentration of 4100 µg/ml under the conditions of the study.

Additionally, a mammalian cell mutation test with mouse lymphoma L5178Y cells (study 2333MV) was conducted at concentrations up to 193 µg/ml ± S9. No precipitation up to the top concentrations could

be observed. RTG at the highest concentration were between 10 – 20 % and all cultures analysed were negative for inducing chromosomal aberrations (chromosomal aberrations, polyploidy, endoreduplication) or an increase in mutant frequency with or without metabolic activation under the conditions of the study.

The negative and positive controls in both studies were inside the historical control data of the study facility.

In vivo

In the in vivo studies, clinical signs of toxicity observed during treatment confirmed exposure to capivasertib.

In the first rat bone marrow micronucleus assay (study 2718QR), capivasertib revealed an increase in the number of micronucleated PCEs at the highest dose tested, which corresponded to the MTD (150 mg/kg) in repeat-dose toxicity studies in rats. A subsequent kinetochore labelling of micronucleated PCEs according to Hayashi 2000 and the IWGTP (study 2759KV) revealed that the majority (86%) of micronuclei induced in the bone marrow were kinetochore positive, indicative of an aneugenic (chromosome loss) thresholded mode of action. The NOEL was 75 mg/kg.

In contrast to the previous rat bone marrow micronucleus assay, in the second assay (study 4075QR) capivasertib revealed no increase in the number of micronucleated PCEs as compared to vehicle up to the MTD of 150 mg/kg in male rats. The negative and positive controls in both studies were inside the historical control data of the study facility. In both assays, no bone marrow toxicity was observed.

Based on toxicokinetic data (AUC) determined in repeat-dose toxicity studies in rats, in the first assay a margin of exposure of approximately ≤ 1 (75 mg/kg) and in the second assay between 1 and 2 at the MTD (150 mg/kg) compared to the clinical exposure was achieved.

In an in vivo COMET assay, no statistically significant increases in percent tail intensities could be observed. Therefore, capivasertib was negative for an increase in DNA damage, up to the MTD in rats (150 mg/kg). Due to the small number of studies (COMET) of the testing facility, the vehicle control group mean was slightly above the historical control value whereas the positive control was inside the historical control data.

Based on toxicokinetic data (AUC) determined in repeat-dose toxicity studies in rats, a margin of exposure of approximately between 1 and 2 at MTD (150 mg/kg) compared to the clinical exposure was achieved.

In conclusion, capivasertib showed no mutagenic or genotoxic potential in vitro. When dosed orally to rats, capivasertib induced micronuclei in the bone marrow via an aneugenic mode of action.

2.5.4.4. Carcinogenicity

No carcinogenicity studies have been submitted in support of this application.

Neither pre-neoplastic nor neoplastic lesions were observed in chronic toxicity studies in rats and dogs up to the highest doses tested. Reversible liver hypertrophy in rats and hypertrophy/hyperplasia of the pancreatic islet cells in rats and dogs were caused by the known PD activity of PI3K/AKT inhibitors. Capivasertib was genotoxic at approximately clinical exposures in a rat bone marrow micronucleus assay with an aneugenic mode of action.

2.5.4.5. Reproductive and developmental toxicity

No fertility and pre-postnatal development studies have been submitted in support of this application. However, the impact of capivasertib on male fertility was evaluated as part of the 6 month rat toxicity study (study 527477). A modified preliminary study on embryo-foetal development that included an assessment of the littering phase was performed in the rat to cover embryo-foetal development as well as early postnatal survival/growth.

A full paediatric waiver has been granted for capivasertib, therefore no juvenile toxicity study has been conducted.

Capivasertib was administered orally, the therapeutic route of administration.

An overview of the performed reproductive toxicology studies is given in the below table.

Table 5 Overview of reproductive and developmental toxicity studies performed with capivasertib

Study type and duration	Route of administration	Species	Study number (AZ reference number)	GLP compliant
Repeat dose toxicity:				
Six month (including male fertility)	Oral	Rat	527477 (3784PR)	Yes
Reproductive and developmental toxicity:				
Preliminary Embryofetal Development and Pre and Post Natal Study	Oral	Rat	496879 (3783RR)	Yes

The study designs and results are summarised in the below table.

Fertility and early embryonic development

Table 6 Six-month repeat-dose toxicity in rats: male fertility

Study ID / Study type/ GLP	**Species; Number/ group**	**Route & [mg/kg/ d]**	**Dosing period**	**Major findings**	**NOAEL [mg/kg/d]**
Study 527477 Male Fertility assessed in 6 month repeat dose study **GLP**	Han Wistar rat 15/sex/ group	0, 10, 30 and 100 oral	<u>Males:</u> Days 1 to 182 (premating after 70 days of beginning of dosing) <u>Females:</u> untreated	None	**Male NOAEL for gonadal function, mating behaviour and reproductive performance:** 100

The objectives of study 527477 were the evaluation of repeated dose toxicity, the evaluation of the effects of capivasertib on gonadal function, mating behaviour and reproductive performance in male Wistar rats. For each female the time taken to show a positive mating sign and the number of failed opportunities to mate (oestruses passed without a sign of mating) were evaluated.

Oral (gavage) treatment of the male Wistar rat with capivasertib at doses of 10, 50 or 100 mg/kg/day was not associated with any effect on male gonadal function, mating behaviour or fertility in any group.

The lower epididymis, testis and thymus weights all correlated with histology findings observed in these organs. In the absence of histological correlation with the reduced prostate weights, the toxicologically significance was considered to be unclear.

The no observed effect level (NOEL) for gonadal function, mating behaviour and reproductive performance in the male Wistar rat was 100 mg/kg/day.

Toxicokinetics

All TK animals dosed with capivasertib were exposed to capivasertib. Systemic exposure increased in a broadly dose-proportional manner across the respective dose range in males and females (see 6-month repeat dose toxicity in rats in section 2.5.4.2.).

Table 7 Toxicokinetics and multiples to clinical exposure for male fertility in six-month repeat-dose toxicity in rats

Summary of key toxicology findings	Dose level mg/kg/day	Total $AUC_{(0-24)}$ (µmol.h/L)	Multiples to total clinical AUC [a]	Total C_{max} (µmol/L)	Multiples to total clinical C_{max} [b]
6 month rat study (527477)					
NOAEL for males (background testes pathology in 1 male)	10 M F	2.16 2.77	0.06 0.08	0.648 0.997	0.20 0.31
As above for both sexes, plus low white cells (males), higher liver enzymes, glycosylated haemoglobin and polyuria. Pathological changes in bone marrow, thymus, pituitary (males) and males reproductive organs.	100 M 150 F	48.7 41.5	1.44 1.22	10.5 15.3	3.26 4.75

Embryo-fœtal development

Effects on embryo-foetal development and early postnatal survival/growth were assessed in a modified rat embryo-foetal development study, which included a littering phase.

Table 8 Preliminary embryo-foetal development and pre- and post-natal study in rats

Study ID / Study type/ GLP	**Species; Number/ group**	**Route & [mg/kg/ d]**	**Dosing period**	**Major findings**	**NOAEL [mg/kg/d]**
Study 496879 Embryo-foetal-development Study And Post Natal Study **GLP**	Wistar rat 8/females/ Group for Phase 1 and Phase 2 each Satellite group for toxico-kinetics (2-3/group) Phase 1 on GD16 Phase 2 pups on LD 7-8	Phase 1: 0, 10,30 and 150 Phase 2: 0, 10 and 150 oral	Phase 1: (GD 6-16) C-section Day 21 Phase 2 (GD 6-Day 6 of lactation)	<u>Phase 1:</u> <u>≥10 mg/kg/d:</u> ↓ BW gain, ↓ food consumption ↑Maternal blood glucose at day 16 <u>150 mg/kg/d:</u> ↑minor foetal visceral variations, ↑post implantation loss ↑early embryonic deaths ↓ gravid uterine and foetal weights Phase 2: <u>≥10 mg/kg/d:</u> ↓ BW gain, ↓ food consumption ↑Maternal blood glucose at day 16 <u>150 mg/kg/d:</u> ↓ litter and pup weights	Phase 1 Maternal: 30 Embryo-foetal development: 30 Phase 2 Maternal: 10 Embryo-foetal/pre-postnatal: 10

BW = Body weight; GD = Gestation day; ↑ = increase; ↓ = decrease; LD= lactation day

Effects on embryo-foetal development and early postnatal survival/growth were assessed in a modified rat embryo-foetal development study, which included a littering phase. The aim of this study was to evaluate the effect of capivasertib on mated female rats when administered from Day 2 to Day 16 of gestation (Phase 1) or from Day 6 of gestation to at least Day 6 of lactation (Phase 2).

Maternal toxicity (reduced body weight gain, reduced food consumption and increase in blood glucose) was seen at ≥ 10 mg/kg/day. Administration of capivasertib to rats prior to implantation until Day 16 of gestation resulted in minor foetal visceral variations (predominantly foetuses with a left-sided umbilical artery), an increase in post-implantation loss, together with reduced gravid uterine and foetal weights at 150 mg/kg/day.

Administration of capivasertib to dams during gestation and through to early lactation caused a reduction in litter and pup weights at ≥ 10 mg/kg/day. There were no compound-related pup abnormalities up to 150 mg/kg/day.

Exposure to capivasertib was confirmed in suckling pups indicating a potential for excretion in milk.

Based on the results of this study, when capivasertib was administered from Day 2 to 16 of gestation the maternal NOAEL and the embryo-foetal NOEL were considered by the applicant to be 30 mg/kg/day. When capivasertib was administered from Day 6 of gestation to at least Day 6 of lactation the maternal NOAEL and the reproductive NOEL were considered by the applicant to be 10 mg/kg/day.

<u>Toxicokinetics</u>

Table 9 TK results in female rats following oral administration of capivasertib (Phase 1)

Dose level (mg/kg/day)	10	30	150
Day of gestation	**16**	**16**	**16**
Females			
Median t_{max} (range) (h)	0.5 (0.5, 0.5)	0.5 (0.5, 2)	0.5 (0.5, 1)
Mean C_{max} (SD) (µmol/L)	0.655 (0.483)	3.69 (3.15)	5.79 (2.34)
Mean $AUC_{(0-t)}$ (SD) (µmol.h/L)	1.46 (0.216)	6.42 (2.24)	25.6 (9.65)

TK results from pups on lactation day 7-8:

On Day 7-8 of lactation capivasertib was not detected at 2 or 24 h post dose in blood plasma of the majority of pups at 10 mg/kg, whereas, at 150 mg/kg/day capivasertib was quantifiable in the majority of pups; however, concentrations were generally close to the limit of quantification.

Table 10 Exposure to capivasertib and multiples to clinical exposure

Summary of key toxicology findings	Dose level mg/kg/day	Total $AUC_{(0-24)}$ (µmol.h/L)	Multiples to total clinical AUC [a]	Total C_{max} (µmol/L)	Multiples to total clinical C_{max} [b]
Embryofetal development and pre- and post-natal study in the rat (496879)					
Phase 1					
Increased maternal blood glucose on SD 16	10	1.46	0.04	0.655	0.20
As above. Considered maternal NOAEL and embryofetal NOEL	30	6.42	0.19	3.69	1.15
As above plus post implantation loss and reduced gravid uterine and fetal weights.	150	25.6	0.76	5.79	1.80
Phase 2					
Maternal NOAEL and reproductive NOEL	10	ND	-	ND	-
Increased maternal glucose. Reduced litter and pup weights.	150	ND	-	ND	-

Capivasertib potentially caused hyperglycaemia in maternal animals, reduced body weight gain and reduced food consumption at ≥ 10 mg/kg/day in Phase 1 and Phase 2 dams. The NOEL for these changes in general, across both sexes, was 10 mg/kg/day over 1 and 6 months.

Administration of capivasertib prior to implantation until Day 16 of gestation resulted in minor foetal visceral variations, an increase in post-implantation loss, together with reduced gravid uterine and foetal weights. These effects were seen at a dose level of 150 mg/kg/day, which caused maternal toxicity. When capivasertib was administered to pregnant rats at 150 mg/kg/day throughout gestation and through early lactation, there was a reduction in litter and pup weights. At 150 mg/kg/day, capivasertib plasma concentrations in pregnant rats were approximately 0.8 times the exposure in humans at the recommended dose of 400 mg twice daily (based on total AUC).

AKT (serine/threonine specific protein kinase) is a pivotal enzyme regulating cell proliferation, survival, metabolism, protein synthesis and gene expression. Capivasertib is an inhibitor of all 3 isoforms of AKT and therefore the adverse effects observed following administration of capivasertib to pregnant or lactating rats are likely due to the pharmacological action of the compound.

2.5.4.6. Toxicokinetic data

All TK animals dosed with capivasertib were exposed to capivasertib. Systemic exposure increased in a broadly dose-proportional manner across the respective dose range in males and females (see 6-month repeat dose toxicity in rats).

Table 11 Toxicokinetics and multiples to clinical exposure for male fertility in six-month repeat-dose toxicity in rats

Summary of key toxicology findings	Dose level mg/kg/day	Total $AUC_{(0-24)}$ (µmol.h/L)	Multiples to total clinical AUC [a]	Total C_{max} (µmol/L)	Multiples to total clinical C_{max} [b]
6 month rat study (527477)					
NOAEL for males (background testes pathology in 1 male)	10 M F	2.16 2.77	0.06 0.08	0.648 0.997	0.20 0.31
As above for both sexes, plus low white cells (males), higher liver enzymes, glycosylated haemoglobin and polyuria. Pathological changes in bone marrow, thymus, pituitary (males) and males reproductive organs.	100 M 150 F	48.7 41.5	1.44 1.22	10.5 15.3	3.26 4.75

Toxicokinetic data were evaluated not only for capivasertib but also for the main human metabolite, the direct ether glucuronide conjugate.

2.5.4.7. Local tolerance

No stand-alone local tolerance studies have been submitted in support of this application.

2.5.4.8. Other toxicity studies

Studies on impurities

The entire potential for genotoxic impurities of capivasertib generated in the drug substance manufacturing process or produced as a degradation product in the drug substance or drug product were assessed in silico by structure-activity relationship evaluation with DEREK (Nexus 6.1.0) and Leadscope (3.2.5) and an additional expert evaluation of each prediction. In case of a positive forecast, additional in vitro genotoxicity assays (AMES test) were conducted.

Potential impurities and degradation products revealed no genotoxicity potential by structure activity relationship and expert evaluation. These impurities were treated as class 5 impurities according to ICH M7 (R2).'

Phototoxicity

A radiolabelled excretion mass balance and tissue distribution study (KMR012, quantitative whole-body autoradiography) in male pigmented rats revealed distribution of capivasertib to the skin and the eyes (uveal tract) with high affinity for melanin in pigmented tissues.

Capivasertib was reversibly bound to melanin with persistence up to 168 h in the skin and 504 h in the eyes.

Maximum absorption of capivasertib in the UV-vis spectrum was measured at approximately 220 and 288 nm in acetonitrile. The corresponding molar extinction coefficients (MEC) were about 31525 and 18058 $l \times mol^{-1} \times cm^{-1}$ and thus, according to the current ICHS10 guideline photosafety testing is requested.

An in vitro 3T3 NRU phototoxicity tests using Balb/c 3T3 mouse fibroblasts did not demonstrate any phototoxic potential. Further, capivasertib was photostable in a photostability test in accordance with ICH Q1B.

2.5.5. Ecotoxicity/environmental risk assessment

Table 12 Summary of main study results

Substance (INN/Invented Name): capivasertib			
CAS-number (if available): 1143532-39-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log Dow (pH 5) 1.28 log Dow (pH 7) 2.38 log Dow (pH 9) 2.46	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log Kow	2.46	not B according to screening criteria
	BCF	k.A.	
Persistence	DT50 (OECD 308)	DT50 = 24.9 d (20°C)	not P
Toxicity	NOEC fish	1 mg/L	not T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.384	µg/L	> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Koc_{soil} = 21100; 453000 $Koc_{sediment}$ = 3780; 23300 Koc_{sludge} = 702; 1070	Terrestrial studies not triggered
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 2.9/4.57 d $DT_{50, sediment}$ = 32.4/18.8 d $DT_{50, whole\ system}$ = 9.47/ 24.9 d	system I/II; 20°C, data in II not reliable as mass balance incomplete;

		% shifting to sediment = 78.9/57.75 % CO2 = 6.75/7.68 % NER = 73.2/41.2 Transformation products >10%: TP Region 2, increasing till test end TP Region 4, max. 24.4%, day 21, total system			parent + NER on d 21; at test end at test end TPs not identified
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC	27	mg/L	*R. subcapitata*; growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	11	mg/L	*D. magna*; reproduction
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	3.2	mg/L	*P. promelas*; growth/length
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000	mg/L	total respiration
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	893 6869	mg/kg	*C. riparius*; Emergence, o.c. 1.3% normalised to 10% o.c. content

2.5.6. Discussion on non-clinical aspects

Pharmacology

Capivasertib was demonstrated to inhibit all three AKT isoforms, AKT1, AKT2 and AKT3, in a biochemical assay. As a result, capivasertib inhibited the activation of AKT downstream targets, GSK3β, PRAS40 and S6, in various cancer cell lines. In a kinase profiling assay, capivasertib also showed activity on several other targets involved in PI3K/AKT or MEK/ERK signalling. Of them, functional inhibition of p70S6K and PKA was observed but the potency in tumour cells was lower compared to AKT target inhibition.

The predictions of the human population pharmacokinetic model suggest that capivasertib's exposure at the proposed clinical dose and schedule would not lead to PKA inhibition and would not achieve inhibition of p70S6K.

The applicant explained that capivasertib's binding to the AKT kinase domain inhibits phosphorylation of the downstream substrates but does not prevent phosphorylation of AKT itself by the upstream kinases.

In several cancer cell line panels, capivasertib demonstrated the best activity in breast cancer cells. Capivasertib was active in wild-type and *PIK3CA*, *AKT1* and *PTEN* mutated cells but the activity was generally better in altered cell lines. In one panel, there was a statistically significant correlation between sensitivity to capivasertib and mutations in the *PIK3CA* and *PTEN*. Addition of capivasertib to fulvestrant or palbociclib increased the efficacy in palbociclib-naive and palbociclib-resistant ER+ PI3Kα mutant cell lines compared to the single agent treatments.

The major human metabolite AZ14102143, an ether glucuronide of capivasertib, was pharmacologically inactive as it had no effect on phosphorylation of AKT downstream targets.

Oral capivasertib inhibited tumour growth in various mouse xenograft models including patient-derived ER+ breast cancer xenografts in a dose-dependent fashion. This was accompanied by the inhibition of phosphorylation of AKT downstream targets in a time- and dose-dependent manner demonstrating a pharmacodynamic effect at clinically achievable plasma drug levels. Combination of capivasertib with fulvestrant showed improved efficacy compared to single agents in *PIK3CA*, *AKT1* and *PTEN* mutated models and also in tumours without alterations, although generally better efficacy on the combination was observed in altered models. Unexpectedly, there was a significant increase in AKT phosphorylation. The applicant explained that capivasertib binding to AKT kinase domain inhibits phosphorylation of the downstream substrates but does not prevent phosphorylation of AKT itself by the upstream kinases. A dose- and time-dependent increase in blood glucose levels was also noted in xenograft models, which is consistent with the results of other studies.

The impact of dosing schedule on capivasertib's efficacy was evaluated in BT474c breast cancer xenografts in mice but with different results. The applicant explained the variability observed across all the experiments performed to determine whether equivalent efficacy could be achieved between a range of intermittent doses and a continuous dose of capivasertib. Therefore, data from individual experiments should not be viewed in isolation but rather as a component part of the full comparison of intermittent versus continuous dosing.

The overall conclusion drawn from the whole data set to inform the clinical dose setting was that intermittent dosing could be as effective as continuous when taking into the account the total dose given. Whilst in some experiments 300mg/kg QD 4 days on 3 days off was used, this was modified to 150 or 130mg/kg BID as this was considered to be a more clinically achievable regimen. These principles were adopted in the dose escalation performed in the early clinical development.

Secondary pharmacodynamics screening revealed significant activity on 7 targets with IC_{50} values between 6.06 and 62.3 µM. These IC_{50} values are more than 8.4-fold higher than the unbound clinical Cmax of 0.717 µM and the interactions with these targets are thus not considered clinically relevant. ROCK1 was also identified as a potential target with the IC_{50} value of 0.47 µM. This concentration is within the clinical range but capivasertib had no effect on the downstream targets of ROCK. This interaction is therefore not considered clinically relevant. At 100 µM capivasertib inhibited voltage-gated cardiac ion channels hCav3.2 and hNav1.5 by 25.5% and 29.6%, respectively, in an electrophysiological assay. This finding has no clinical relevance as 100 µM by far exceeds plasma levels of capivasertib in patients.

Capivasertib exerted concentration-dependent hERG channel activity with the IC_{50} value of 73.0 µM. This is more than 100-fold of the unbound clinical Cmax. In male Beagle dogs, oral dosing of 30 and 40 mg/kg capivasertib led to a reversible reduction in systolic and diastolic blood pressure and heart rate and caused a sustained statistically significant prolongation of the QT interval. Both glucose and insulin levels were increased after administration of 30 and 40 mg/kg. The NOAEL was set at 5 mg/kg. The unbound Cmax in dogs at the NOAEL was 0.28 µM, which is below the expected clinical exposure.

Cardiovascular effects (QTc interval prolongation, increased cardiac contractility, and decreased blood pressure) were seen in dogs at plasma concentrations approximately 1.4 to 2.7 times the expected clinical exposure in humans at the recommended dose of 400 mg twice daily (based on unbound Cmax).

In rats, decreased spontaneous activity and decreased touch response as well as reduced body weight were observed at the doses of 100 and 150 mg/kg. The NOEL in this CNS study was considered to be 30 mg/kg. At this dose level, the rat unbound Cmax was 0.65 µM, which is in the range of the expected clinical Cmax. There were no effects on respiratory parameters in rats up to 150 mg/kg, which was the NOEL. The unbound animal Cmax at the NOEL was 3.8 µM being 5.3-fold the expected human exposure. Capivasertib led to a statistically significant inhibition of gastric emptying at 100 and 150 mg/kg and a significant decrease in intestinal transit at 150 mg/kg. The NOEL in the gastrointestinal study was determined as 30 mg/kg. At this dose level, the exposure was comparable to the clinical exposure. In addition, rats experienced marked glucosuria with concurrent diuresis after oral administration of 100 and 150 mg/kg capivasertib.

Pharmacokinetics

Capivasertib is likely to have a low to moderate fraction absorbed in vivo in humans. The absorption was investigated in the toxicokinetic part of the toxicology studies as well as in several pharmacodynamic and the pivotal safety pharmacology studies. No stand-alone pharmacokinetic studies were conducted, which is considered acceptable.

Plasma protein binding of [^{14}C]-capivasertib decreased in the following order: mouse > human ≈ dog > rat. The free fraction of capivasertib in human plasma was determined as 22.3% with the main binding partner being human serum albumin. The unbound fraction of the major human metabolite AZ14102143 was 36.8%. The mean proportion of [^{14}C]-capivasertib associated with blood cells in vitro was 61%. The unbound fraction of capivasertib in human liver microsomes and in human hepatocytes was 0.622±0.031 and 0.647 ± 0.019, respectively. Non-specific binding of capivasertib to the equilibrium dialysis apparatus (8%) was observed in one study but considered acceptable by the applicant. In other protein binding studies, non-specific binding was indeed not specifically investigated. However, high stability and high recovery determined in those studies point at low non-specific binding. This is considered acceptable.

In rats administered [^{14}C]-capivasertib, radioactivity distributed to excretory organs and was associated with melanin. Metabolism of [^{14}C]-capivasertib was faster in rat and dog hepatocytes than in human hepatocytes. The major metabolite in dog and human was an ether glucuronide conjugate of [^{14}C]-capivasertib. The major metabolites in rat was a sulfate conjugate. In vivo, unchanged capivasertib was the main component of the drug-related material in plasma and excreta of rats. In male rats, the major metabolites of capivasertib were oxidation products, in female rats it was a sulfate conjugate. The major human metabolite, glucuronide AZ14102143, was only detected in bile duct-cannulated rats. A metabolism study in the dog would have been expected to be conducted as part of the non-clinical programme for capivasertib however such lack is considered acceptable. The applicant justified the absence of a metabolism study in the dog by arguing that ether glucuronides are more water soluble than the parent compound and are also pharmacologically inactive and also that according to ICH S9, no need for such evaluation is generally warranted (in some cases, metabolites that have been identified in humans have not been qualified in non-clinical studies).

Heterologously expressed CYP2D6 also appeared to be involved in the formation of the mono-oxygenated metabolites but this was not confirmed in the inhibitory antibody experiments.

The inhibition of CYP1A1 in human liver microsomes was not studied due to a very low expression of this isoform in liver and extrahepatic tissues.

In intact rats, capivasertib was predominantly excreted via faeces. In bile-duct cannulated rats, biliary excretion represented the major proportion of total elimination.

Toxicology

One consequence of the inhibition of the PI3K/AKT pathway is hyperglycaemia due to changes in the insulin-mediated glucose homeostasis, which depends on PI3K signalling. Thus, increased levels of glucose and insulin were seen in both rats and dogs. Although hyperglycosylation is considered as the result of the pharmacodynamic effect of capivasertib, a warning regarding the risk of hyperglycaemia with capivasertib, including the potential need to intensify anti-diabetic treatment and closely monitor patients with diabetes mellitus has been included in section 4.4. of the SmPC.

Further toxicities included increased levels of fructosamine (rats), glycosylated haemoglobin (rats and dogs), glycogen accumulation in the liver (rats and dogs), liver hypertrophy (rats), hypertrophy/hyperplasia or vacuolation of the pancreatic islet cells (rats and dogs) and glucosuria. All of them were also related to the glucose perturbation.

An additional on-target adverse event was polyuria in both rat studies with increased water consumption accompanied by glucosuria and proteinuria. These changes were not present at the end of the recovery period in the 1-month study. However, additional kidney changes (decreased cell size/nuclear crowding of tubular cells; decreased kidney weight and size) were present in the 6-months rat study. As the study with the longer duration did not include a recovery period the findings are difficult to interpret. However, AKT is known to play a role in proximal tubular glucose and phosphate transport.

Increases in cardiac contractility were observed in the dog telemetry and dog 1-month toxicity studies. These findings were not present at the end of the recovery period but the underlying mechanism is unknown. The applicant argued that QT prolongation is not considered to be clinically relevant since the findings occurred at exposures higher than the clinically therapeutic dose of 400 mg twice daily. It is endorsed that the margin of exposure is higher than for the observed hyperglycaemia. However, a 2-fold exposure based on AUC cannot be regarded as high enough to be interpreted as clinically irrelevant. In addition, the combination of capivasertib with drugs having QT prolongation potential might result in adverse events in the clinical setting. Thus, given the lack of information with respect to QT prolongation, from a preclinical point of view, a statement has been included in section 4.4 of the SmPC on the clinical consequences of diarrhoea which may include dehydration, hypokalaemia and acute kidney injury which have all, together with cardiac arrhythmias (with hypokalaemia as risk factor) been reported during treatment with capivasertib.

As mentioned in the 2019 CHMP Scientific Advice letter, the connection between inhibitors of the PI3K/AKT/mTOR pathway and effects on individual cardiac ion currents in the development of prolongation of QT interval is an area of active research and it is acknowledged that cardiac effects were not noticed in the 9-months dog study and no safety signal in clinical studies were observed; however this study did not include a recovery group (similar to the long-term rat study). Furthermore, concomitant administration of capivasertib with other drugs that are known for QT prolongation may enhance risk factors for TdP and the QT toxicity. A warning about cardiovascular effects observed in dogs has been included in section 5.3 of the SmPC.

The relevant information concerning genotoxicity is indicated in the relevant section 5.3 of the SmPC.

Capivasertib had no effect on fertility in male rats. Effects on female fertility have not been studied in animals. In females, repeat-dose toxicity studies have reported some weight changes of the uterus in rats which were attributed to oestrous cycle changes. Histopathological examination conducted in rat and dog studies did not show any treatment-related effects on female reproductive organs, which may be indicative of an adverse effect on female fertility.

Capivasertib caused degenerative changes in the testes in both rats (1-month study) and dogs (1- and 9-month study) with associated findings in the epididymis and a reduction in organ weight. These changes did not recover.

In the one month rat study, there were sex differences in exposure (based on AUC(0-last)) to capivasertib with greater plasma levels in males than females. Measurement of insulin in female animals and measurement of HbA1C levels would have been interesting, but only data from the long-term toxicology studies are available. Nevertheless, it would have been interesting to collect data in the short term toxicology study.

Toxicokinetic data were evaluated not only for capivasertib but also for the main human metabolite, the direct ether glucuronide conjugate. However, such data were only presented for mice. As intact rats do not form the metabolite, the absence of these data in rats is considered acceptable. However, it would have been helpful to generate such data in the dog considering that the glucuronide metabolite was formed in dog hepatocytes and in view of the fact that no meaningful margins of safety were found in the appropriate studies. However, it is acknowledged that, according to ICH S9, no need for such evaluation is generally warranted (*In some cases, metabolites that have been identified in humans have not been qualified in nonclinical studies. For these metabolites, a separate evaluation is generally not warranted for patients with advanced cancer*). Thus, the absence of the toxicokinetic evaluation of the metabolite is considered acceptable.

The major target organs or systems for toxicity were insulin signalling (increased levels of glucose and insulin in rats and dogs), the male reproductive organs (tubular degeneration in rats and dogs), and the renal system in rats (polyuria, decreased tubular epithelial cell size, decreased kidney size and weight). The findings present following 1 month of dosing were largely reversible within 1 month of cessation of dosing. Findings occurred at plasma concentrations lower or similar to those in humans (approximately 0.14 to 2 times) at the recommended dose of 400 mg twice daily (based on total AUC).

Capivasertib was not genotoxic in vitro and did not induce increases in DNA damage in the liver of Han Wistar rats. However, capivasertib was positive in one in vivo micronucleus assay whereas the second test was negative. Kinetochore labelling of micronucleated PCEs revealed an aneugenic threshold mode of action. All mutagenic and potentially mutagenic impurities were assessed for risk according to ICH M7. The relevant information concerning genotoxicity testing is indicated in the relevant section 5.3 of the SmPC.

The carcinogenic potential of capivasertib has not been studied which is in accordance with ICH S9.

Capivasertib caused adverse effects following administration to pregnant or lactating rats (degenerative changes in the testes, hyperglycaemia in maternal animals, increase in post-implantation loss plus reduced gravid uterine and foetal weights).

Regarding impairment of fertility in rats, in the 6-month toxicology study no functional effect on male fertility was demonstrated. However, the sensitivity of mating assays to effects on fertility in rodents is known to be low given the extremely high sperm production in this species and the fact that these animals remain fertile even with sperm reductions of up to 90% (Mangelsdorf et al., 2003), whereas smaller reductions in human fertility parameters might have a greater effect on fertility.

Capivasertib has resulted in testicular toxicity and may impair fertility in males of reproductive potential. Effects on female fertility have not been studied in animals. In females, repeat-dose toxicity studies have reported some weight changes of the uterus in rats which were attributed to oestrous cycle changes. Histopathological examination conducted in rat and dog studies did not show any treatment-related effects on female reproductive organs, which may be indicative of an adverse effect on female fertility.

Preliminary studies on embryonic and foetal development in rats and a pre- and postnatal study have been carried out. The applicant explained that further embryo-foetal development studies were not conducted with capivasertib as it has been shown to be embryolethal. Indeed, post-implantation loss increased at the high dose level in animals treated from GD 2 to GD 16. Historical control data for similar preliminary studies conducted at the same test facility have been provided.

In a rat embryofoetal study, capivasertib caused an increase in post implantation loss, an increase in early embryonic deaths, together with reduced gravid uterine and foetal weights, and minor foetal visceral variations. These effects were seen at a dose level of 150 mg/kg/day which caused maternal toxicity, and where plasma concentrations were approximately 0.8 times the exposure in humans at the recommended dose of 400 mg twice daily (based on total AUC). When capivasertib was administered to pregnant rats at 150 mg/kg/day throughout gestation and through early lactation, there was a reduction in litter and pup weights.

Exposure to capivasertib was confirmed in suckling pups which may indicate the potential for excretion of capivasertib in human milk.

No stand-alone local tolerance studies have been submitted in support of this application. Since the proposed route of administration is oral, this is considered acceptable.

Capivasertib is intended for the treatment of cancer patients with serious and life-threatening malignancies. For indications falling under the scope of ICH S9, the guideline ICH Q3A (R2) should be applied for the control of (potential) mutagenic impurities. In the case of capivasertib, the applicant decided to assess the potential mutagenic impurity profile according to ICH M7 (R2), which is more conservative and therefore acceptable. Therefore, a potential for phototoxicity of capivasertib is considered unlikely.

Capivasertib did not demonstrate any phototoxic potential.

Capivasertib exceeds the Phase I PEC trigger of 0.01 µg/L. A Phase II ERA was provided by the applicant. The logK_{OW} remained below 4.5, thus a PBT assessment is not considered necessary. The data presented by the applicant show that capivasertib does not present an environmental risk following patient use.

2.5.7. Conclusion on the non-clinical aspects

The non-clinical data package evaluating the pharmacology and toxicity of capivasertib is considered acceptable to support the marketing authorisation.

Capivasertib is not a PBT substance. Considering the above data, capivasertib is not expected to pose a risk to the environment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 13 Studies contributing PK and/or PD data

Study number (name) Study title	DCO date	Objectives of the study	Study design and type of control	Route of administration and dosing regimen
D3615C00001 (CAPItello-291) 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)	Ongoing DCO1: 15 August 2022	Efficacy, safety, PK, HRQoL	Double-blind, randomised, placebo-controlled	Capivasertib/placebo 400 mg oral BD Days 1 to 4 in each week of a 28-day treatment cycle. Fulvestrant 500 mg on Day 1 of Weeks 1 and 3 of Cycle 1, and then on Day 1, Week 1 of each cycle.
FTIH Study (D3610C00001) A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Anti-Tumour Activity of Ascending Doses of AZD5363 under Adaptable Dosing Schedules in Patients with Advanced Solid Malignancies	Part A and Part B: 07 July 2014 Part C: 15 September 2016 Part D: 22 August 2017 Part E: 07 August 2018 Part F: 26 April 2019	Safety, tolerability, efficacy, PK	Open-label	Parts A and B: Schedule 1: continuous dosing, starting dose 80 mg BD. Dose range: 80 mg to 600 mg BD. Schedule 2: intermittent dosing, 4 days on, 3 days off (480 and 640 mg BD) OR 2 days on, 5 days off (640 and 800 mg BD) Schedule 3 (optional; not conducted): alternative intermittent schedule. Parts C and D: Intermittent dosing 480 mg BD 4 days on, 3 days off. Parts E and F: Intermittent dosing 400 mg BD 4 days on, 3 days off in combination with fulvestrant at 500 mg IM on Days 1, 15, 29, and once monthly thereafter.

Table 14 Overview of the clinical studies evaluating efficacy of capivasertib in subjects with HR+/HER2- advanced/metastatic breast cancer

Study ID **Number of Sites/Countries** **Study Start/ Status**	**Study Design**	**Treatments Administered**	**Efficacy Objectives**	**Number of Subjects (Actual)**	**Study Population**	**Efficacy Endpoints**
Pivotal study						
D3615C00001 (CAPItello-291) 181 centres in 19 countries (Europe: Belgium, France, Germany, Hungary, Italy, Poland, Russian Federation, Spain, UK ROW: Argentina, Australia, Canada. China, Israel, Japan, Peru, South Korea, Taiwan, US) FPFV: Apr 2020 DCO: Aug 2022 Complete for PFS, ongoing for OS	randomised, double-blind, placebo-controlled phase 3 study event-driven	exp. arm (n=355): capivasertib 400 mg BD PO (dosed D1-D4 in a weekly dosing schedule) comp. arm (n=353): placebo (as capivasertib) backbone therapy: fulvestrant 500 mg IM once per 28 days (+ loading dose on C1D15) in addition in pre-/ peri-menopausal women LHRH agonist (as to local guidelines)	primary: compare the effect of capivasertib relative to placebo both as add-on to fulvestrant by assessment of PFS in the *overall population* and in the PIK3CA/AKT1/PTEN altered population. key secondary: compare the effect of capivasertib relative to placebo both as add-on to fulvestrant by assessment of OS and ORR in the *overall population* and in the PIK3CA/AKT1/PTEN altered population.	708 patients (incl. 289 patients with PIK3CA/AKT1/PTEN alteration) 1:1 randomisation to either capivasertib or placebo	adult patients with locally advanced (inoperable) or metastatic HR+/HER2- breast cancer following recurrence or progression on or after aromatase inhibitor therapy, with or without prior use of a CDK4/6 inhibitor	primary: PFS (INV) in the *overall population* AND PFS (INV) in the PIK3CA/AKT1/PTEN altered subgroup key secondary: OS in the *overall population* AND OS in the PIK3CA/AKT1/PTEN altered subgroup

Study ID Number of Sites/Countries Study Start/ Status	Study Design	Treatments Administered	Efficacy Objectives	Number of Subjects (Actual)	Study Population	Efficacy Endpoints
Supportive study (externally sponsored)						
FAKTION 19 centres, all in UK First patient screened: March 2015 DCO (primary analysis): Jan 2019 Phase Ib: Closed Phase II: Ongoing (primary results reported)	Phase 1b part (n=8): Dose-escalation safety run-in Phase 2 part: randomised (1:1), double-blind, placebo-controlled proof-of-concept	*Phase 2 part* exp. arm (n=69): capivasertib 400 mg BD PO (dosed D1-D4 in a weekly dosing schedule) comp. arm (n=71): placebo (as capivasertib) backbone therapy: fulvestrant 500 mg IM once per 28 days (+ loading dose on C1D15)	*Phase 2 part* Primary: To assess the relative anti-tumour activity of capivasertib vs placebo both as add-on to fulvestrant in terms of PFS using RECIST 1.1 Secondary: To examine the relative efficacy of capivasertib vs placebo both as add-on to fulvestrant in subpopulations of patients ± activation of the tumour PI3K/PTEN pathway	*Phase 2 part:* 140 patients (1:1 randomisation to either capivasertib or placebo)	*Phase 2 part* post-menopausal women with locally advanced (inoperable) or metastatic ER+/HER2- breast cancer following recurrence or progression on or after aromatase inhibitor therapy, including no patients with a prior CDK4/6 inhibitor	*Phase 2 part* Primary: PFS (INV) in the *overall population*

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Absorption

Healthy volunteers

In Part 1 of study D3614C00007 ("A Phase I Study to Investigate the Absolute Bioavailability, Absorption, Metabolism, Distribution and Excretion of [^{14}C]AZD5363 (Capivasertib) in Healthy Male Subjects" the absolute bioavailability and the PK parameters of a single unlabelled oral dose and a radiolabelled intravenous (IV) microdose of Capivasertib was investigated.

Table 15 Geometric mean (geometric CV%) plasma pharmacokinetic parameters following a single oral dose of 400 mg capivasertib ((2 × 200 mg film-coated tablets): pharmacokinetic analysis set - part 1

Parameter	Capivasertib [N =6]

t_{lag} [a] (h)	0.000 (0.00-0.00)
[a] t_{max} (h)	1.742 (0.75-3.00)
C_{max} (ng/mL)	547 (29.7)
AUC_{0-t} (ng.h/mL)	2950 (26.1)
AUC_{0-t}/D (ng.h/mL/mg)	7.39 (26.1)
AUC (ng.h/mL)	2990 (25.6)
AUC/D (ng.h/mL/mg)	7.49 (25.6)
$T_{1/2}$ (h)	12.864 (11.3)
CL/F (L/h)	134 (25.6)
Vz/F (L)	2480 (23.3)
MRT_{0-t} (h)	9.164 (14.6)
MRT (h)	10.139 (15.2)
MAT (h)	4.655 (31.5)
F (%)	28.549 (22.0)

a Median (range)

Table 16 Geometric mean (geometric CV%) plasma pharmacokinetic parameters following a single intravenous infusion of 100 µg [^{14}C]AZD5363 (capivasertib): pharmacokinetic analysis set – part 1

Parameter	[^{14}C]AZD5363 (capivasertib) [N=6]
[a] t_{max} (h)	0.275 (0.12-0.33)
C_{max} (pg/mL)	2600 (21.8)
AUC_{0-t} (pg.h/mL)	2540 (15.0)
AUC_{0-t}/D (pg.h/mL/µg)	25.4 (15.0)
AUC (pg.h/mL)	2620 (15.0)
AUC/D (pg.h/mL/µg)	26.2 (15.0)
$T_{1/2}$ (h)	6.864 (5.8)
CL (L/h)	38.1 (15.0)
V_z (L)	378 (17.9)
V_{ss} (L)	205 (15.8)
MRT_{0-t} (h)	4.37 (9.3)
MRT (h)	5.38 (8.0)

[a] Median (range)

The absolute bioavailability of Capivasertib following a 400 mg Capivasertib oral dose was 29%.

Table 17 Capivasertib statistical analysis results – assessment of bioavailability: pharmacokinetic analysis set – part 1

					Pairwise Comparisons		
Pharmacokinetic Parameter	**Regimen**	**N**	**Adj Geo Mean**	**90% CI**	**Pair**	**Ratio**	**90% CI**
AUC/D (ng.h/mL/mg)	Oral	6	7.49	(6.40, 8.75)			

AUC/D (pg.h/mL/ug)	IV	6	26.2	(22.4, 30.7)	Oral / IV	28.55	(23.87, 34.15)

Note that for the purpose of this comparison, although oral AUC/D is presented in ng.h/mL/mg units and IV is presented in pg.h/mL/µg units, these are equivalent in magnitude.

Subjects with advanced solid malignancies

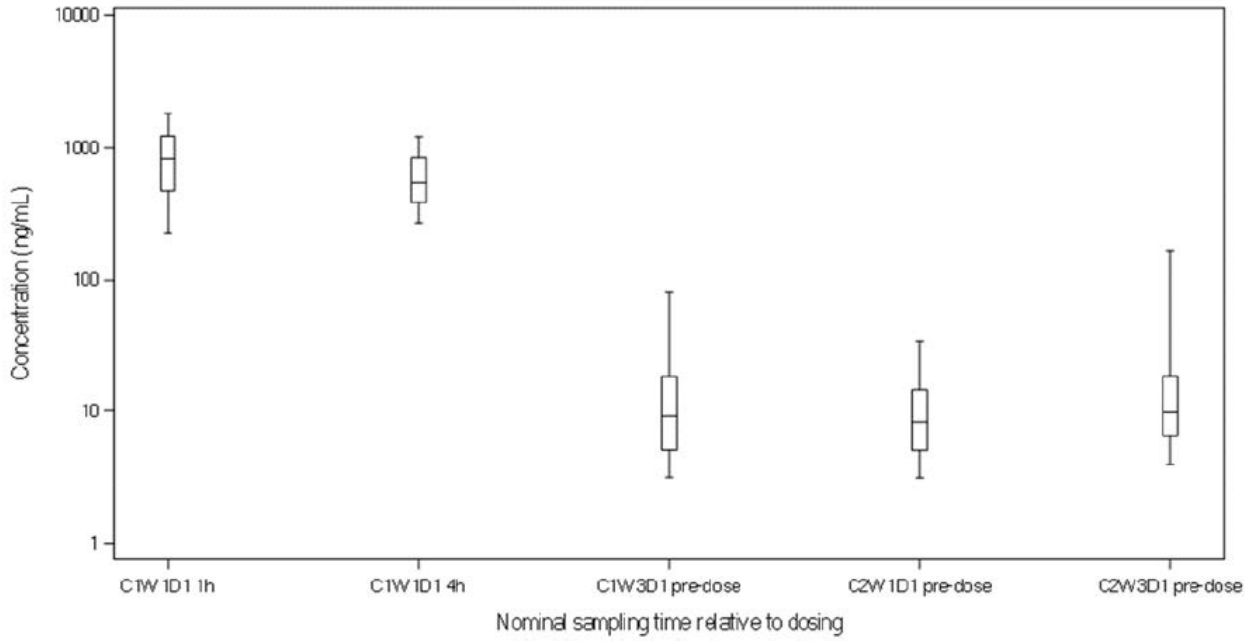
Study D3610C00001 (FTIH) was a Phase I, open-label, multicentre study with 6 parts (Parts A, B, C, D, E, and F) to assess the safety, tolerability, preliminary anti-tumour activity and characterise the PK of capivasertib when administered orally in patients with advanced solid malignancies. Parts A to D investigated capivasertib monotherapy and Parts E and F investigated capivasertib + fulvestrant.

Following single oral doses of capivasertib, median tmax values ranged from 1.00 to 2.17 hours. The apparent terminal half-life was approximately 10 hours (range: 6.85 to 15.0 hours) and was independent of dose.

Taking into consideration the small cohort sizes and the data variability, the gmean Cmax and AUC data from patients that had received 80 mg, 160 mg, 240 mg, 320 mg, 400 mg, 480 mg, 600 mg, 640 mg, or 800 mg AZD5363 appeared to be generally dose-proportional.

In the pivotal phase III study D3615C00001 (CAPItello-291 study), PK samples were collected at Cycle 1 Week 1 Day 1 post-dose at 1 hour and 4 hours; and pre-dose at Cycle 1 Week 3 Day 1, cycle 2 Week 1 Day 1, and Cycle 2 Week 3 Day 1 (sparse sampling). Capivasertib plasma concentration variables Ctrough (pre-dose), C1h, C4h (post-dose) were analysed in the Overall Population (PK Analysis Set). Additionally, rich PK sampling in a subpopulation of Japanese patients was performed pre-dose and up to 12 hours post-dose at Cycle 1 Week 1 Day 1, and pre-dose at Cycle 1 Week 3 Day 1, Cycle 2 Week 1 Day 1, and Cycle 2 Week 3 Day 1. Capivasertib plasma concentration variables, Ctrough (pre-dose), C1h, and C4h (post-dose) were analysed in the Overall Population. The AUC0-12h, Cmax and tmax were derived using a noncompartmental PK analysis (NCA) in a subpopulation of 6 Japanese patients with rich PK sampling (Japan Intensive PK Analysis Set).

Figure 2 Box-plot of plasma concentration (ng/mL) of capivasertib versus time (PK analysis set)



The middle line in the box represents the median. Upper and lower border of the box represent upper and lower quartile, respectively.
The whiskers represent the ranges for the bottom 25% and the top 25% of the data values, excluding outliers (values > 20 times the IQR).
All data from C1W1D1 Japanese Intensive PK patients are excluded.

In the subpopulation of Japanese patients, following a single oral dose, Capivasertib was rapidly absorbed with a median tmax of 1.49 hours. The geometric mean Cmax was 1697 ng/mL and the geometric mean AUC0-12h was 6050 ng•h/mL. The variability was moderate (55.1% CV and 44.6% CV, respectively) (n = 6).

Capivasertib is therefore rapidly absorbed with peak concentration (Cmax) observed at approximately 1-2 hours in patients. The mean absolute bioavailability is 29%.

Accumulation

Following intermittent dosing of 480 mg BD 4 days on, 3 days off in clinical study D3610C00001, the mean AUC0-12h on Day 4 was 1.76-fold (range 0.92 to 2.52) that of the AUC0-12h on the first day of dosing.

Steady State

Due to the small numbers of patients that had calculable Cmin ratios (30 patients from the 90 patients in the PK dataset) and the data variability, it was not possible to use these data to demonstrate that steady state had been achieved for all cohorts and schedules. The ratios of Cmin; Day 15 to Day 7 (continuous dosing), Day 11 to Day 4 (4 on/3 off intermittent dosing schedules) and Day 9 to Day 2 (2 on/5 off intermittent dosing schedules) were generally supportive of PK steady state: values ranged from 0.394 to 4.24 with g_{mean} values, where calculable, being close to unity (values ranged from 0.8051 to 1.457). Based on the $t_{1/2}$ of AZD5363 (around 10 hours) it would be expected to take about 2 days to achieve steady state.

Given the findings from the Cmin ratio data and the absence of a clear temporal change in pharmacokinetics, it was concluded that the data were supportive of steady state being approached during the on-drug phase of all schedules tested.

BCS-class

Capivasertib was considered to be a BCS class 4 compound (low solubility/low permeability) according to the BCS and available solubility, in vitro permeability, and absolute bioavailability data.

Bioequivalence

During the course of the development programme, 3 different immediate release formulations were used. The details of the composition of these formulations and further information are described in detail in section 2.4.3.

Initial Phase I and some of the Phase II clinical studies were performed using a capsule presentation ('Phase I capsule') which consisted of a hard capsule shell filled with capivasertib drug substance. For one of the Phase I clinical studies, the Phase II clinical studies, and the relative bioavailability study, an immediate release tablet presentation was developed ('Phase II tablet'). The Phase III/commercial tablet ('Phase III/commercial tablet') is an optimised film-coated tablet formulation. The commercial capivasertib film-coated tablets are quantitatively identical to the Phase III clinical film-coated tablets but are differentiated through use of debossing; the clinical tablets are plain, while the commercial tablets will be debossed.

Potential differences were investigated in study D3610C00007 (A Phase I, Open-Label, Multicentre Study to Compare Two Dosage Formulations of AZD5363 and to Establish the Effect of Food on the Pharmacokinetic Exposure, Safety and Tolerability of AZD5363 in Patients with Advanced Solid Malignancies (OAK)).

Table 18 Summary of PK parameters of AZD5363 (Part A) (Pharmacokinetics analysis set)

Treatment/ Condition	Visit	Summary statistic	$C_{ss,max}$ (µg/mL)	$C_{ss,min}$ (µg/mL)	AUC_{ss} (h*µg/mL)	CL_{ss}/F (L/h)	$t_{ss,max}$ (h)
AZD5363 480 mg bd 4on/3off/Tablet	Cycle 1 Day 4	n	11	11	11	11	11
		Geometric mean	1779	192.6	8536	NC	NC
		CV (%)	46.24	55.60	47.69	NC	NC
		Arithmetic mean	1934	218.4	9323	61.79	NC
		sd	792.5	121.1	3905	28.60	NC
		Med	1920	197	9410	NC	1.03
		Min	848	94.9	4050	31.6	0.58
		Max	3210	506	15200	119	2.00
AZD5363 480 mg bd 4on/3off/Capsule	Cycle 1 Day 11	n	11	11	11	11	11
		Geometric mean	1745	271.5	9445	NC	NC
		CV (%)	40.20	57.66	44.61	NC	NC
		Arithmetic mean	1865	308.2	10230	55.26	NC
		sd	700.9	166.1	4251	24.69	NC
		Med	1720	313	9180	NC	2.00
		Min	901	106	4280	26.8	1.00
		Max	3160	710	17900	112	4.00

Abbreviations: AUCss, area under the curve at steady state; bd, twice daily; CLss/F, plasma clearance at steady state; Css,max, maximum concentration study treatment in plasma at steady state after multiple dosing; Css,min, minimum concentration study treatment in plasma at steady state after multiple dosing; CV, coefficient of variation; Max, maximum; Med, median; Min, minimum; sd, standard deviation; tss,max, terminal steady state time to Cmax; NC, not calculated.

Table 19 Geometric mean and 90% CI for ratio of tablet to capsule – tablet formulation comparison (Part A) (Pharmacokinetics analysis set)

	Tablet		Capsule			
Pharmacokinetic parameter	n	LS Mean	n	LS Mean	90% CI of Point estimate of geometric mean ratio of tablet to capsule	geometric mean ratio of tablet to capsule	Intra-patient variability (%)
AUC_{ss} (h*µg/mL)	11	9.05	11	9.15	0.90	0.77, 1.06	20.29
$C_{ss,max}$ (µg/mL)	11	7.48	11	7.46	1.02	0.86, 1.20	21.75

Abbreviations: AUC_{ss}, area under the curve at steady state; CI, confidence interval; $C_{ss,max}$, maximum concentration study treatment in plasma at steady state after multiple dosing; LS, least squares.

Influence of food

Clinical studies D3610C00007 and D3614C00005 investigated the potential influence of food.

In Part B of study D3610C00007, during the first week of Cycle 1, patients were dosed with the Phase II tablet formulation, according to standard fasting restrictions (i.e. no food from 2 hours before to 1 hour after dosing), with the exception of Day 4. On Day 4, following an overnight fast (minimum of 8 hours), patients received their first dose with no food permitted for 4 hours post-dose.

During the second week of Cycle 1, patients received capivasertib according to the same schedule and fasting restrictions as for Week 1 with the exception of Day 11 on which, following an overnight fast

(minimum of 8 hours), patients received their first daily dose 30 minutes after starting a standardised meal containing 605 kcal, of which 24% (36 g) were proteins, 26% (18 g) fat, and 50% (76 g) carbohydrates. No further food was permitted for 4 hours post-dose. PK blood samples were taken at Cycle 1 Days 1, 4, 8 and 11.

Table 20 Geometric mean and 90% CI for ratio of fed to fasted – food effect (Part B) (Pharmacokinetics analysis set)

Pharmacokinetic parameter	Fed n	Fed LS Mean	Fasted LS n	Fasted Mean	Point estimate of geometric mean ratio Fed to Fasted	90% CI of geometric mean ratio of Fed to Fasted	Intra-patient variability (%)
AUC_{ss} (h*µg/mL)	9	9.00	9	9.12	0.89	0.76, 1.05	19.03
$C_{ss,max}$ (µg/mL)	9	7.12	9	7.52	0.67	0.55, 0.82	22.98

Abbreviations: AUC_{ss}, area under the curve at steady state; CI, confidence interval; $C_{ss,max}$, maximum concentration study treatment in plasma at steady state after multiple dosing; LS, least squares.

Study D3614C00005 (An Open-label, Randomized, Crossover Study in Healthy Subjects to Evaluate the Effect of Food and Acid Reducing Agent(s) on the Pharmacokinetics of Capivasertib) was a Phase I, 2-part, adaptive, open-label, randomised, crossover study to evaluate the effect of food and acid-reducing agents on the PK of capivasertib in healthy subjects.

Table 21 Food/PPI Study (D3614C00005): statistical comparison of key PK parameters (PK analysis set)

Treatment comparison	GMR (90% CI)		
	AUC_{inf}	AUC_{last}	C_{max}
Part 1: High-fat, high-calorie meal versus overnight fast	1.323 (1.223, 1.431)	1.327 (1.226, 1.436)	1.233 (1.078, 1.410)
Part 1 and Part 2: High-fat, high-calorie meal versus partially fasted	1.132 (0.9917, 1.293)	1.134 (0.9919, 1.297)	0.8536 (0.6977, 1.044)
Part 2: Low-fat, low-calorie meal versus overnight fast	1.144 (1.048, 1.249)	1.150 (1.050, 1.260)	1.208 (0.9864, 1.479)
Part 2: Low-fat, low-calorie meal versus partially fasted	0.9590 (0.8760, 1.050)	0.9578 (0.8719, 1.052)	0.8647 (0.7024, 1.064)

When capivasertib was administered after a high-fat, high-calorie meal (approximately 1000 kcal), the fed to fasted ratio was 1.32 and 1.23, for AUC and C_{max}, respectively, compared to when given after an overnight fast. When capivasertib was administered after a low-fat, low-calorie meal (approximately 400 kcal), the exposure was similar to that after fasted administration with fed to fasted ratios of 1.14 and 1.21, for AUC and C_{max}, respectively. Co-administration with food did not result in clinically relevant changes to the exposure.

Distribution

The geometric mean (geometric CV%) volume of distribution (V_{ss}) was 205 L (15.8%) after IV administration to healthy subjects.

Based on non-clinical data, capivasertib is not extensively bound to plasma proteins (percentage unbound 22.3%). The plasma to blood ratio was 0.714.

Elimination

In FTHI study D3610C00001 the mean terminal half-life in patients was 9.9 hours after a single dose of capivasertib 400 mg, ranging from 8.4 to 11.2 hours across the doses and schedules investigated (based on NCA). In ADME study D3614C00007, the geometric mean apparent terminal half-life was 5.4 h for plasma total radioactivity and 12.3 h for capivasertib.

The mean total plasma clearance is 38.1 L/h after a single IV administration to healthy subjects.

Population PK analysis estimated mean total oral plasma clearance at 60.0 L/h after single oral administration, with an inter-individual variability of 36.2%. Clearance was estimated to decrease by 8% after 7 days of repeated dosing of 400 mg BD.

Based on population PK analysis, the effective half-life after multiple dosing is estimated to be 8.3 hours.

Renal clearance contributed to 21% of the total clearance in healthy subjects and the geometric mean renal clearance of capivasertib was 8.30 L/h.

Following single oral dose of 400 mg, the mean total recovery of radioactive dose was 45% from urine and 50% from faeces. Renal clearance was 21% of total clearance.

In study D3610C00001, taking plasma protein binding of AZD5363 into account, renal clearance was high compared to the glomerular filtration rate indicating that renal excretion may have an active component. The median tmax for capivasertib and plasma total radioactivity was 2.07 h.

Metabolism

Results from in vitro studies suggest that capivasertib is primarily metabolised by CYP3A4 and UGT2B7 enzymes. Human metabolites of capivasertib were detected and quantified in Day 8 AUC pooled plasma samples from patients receiving 400 mg BD from the FTIH study D3610C00001. The major metabolite in human plasma was identified as an ether glucuronide (AZ14102143) that accounted for 83% of total drug-related material using nuclear magnetic resonance spectroscopy, and was inactive against AKT. A minor oxidative metabolite ("+3[O]") was detected and quantified at much lower levels (2%), while capivasertib accounted for 15% of total circulating drug-related material.

No active metabolites have been identified.

In urine, the major response was characterised as the ether glucuronide, and it was estimated that it represented 19% to 37% of the dose in urine.

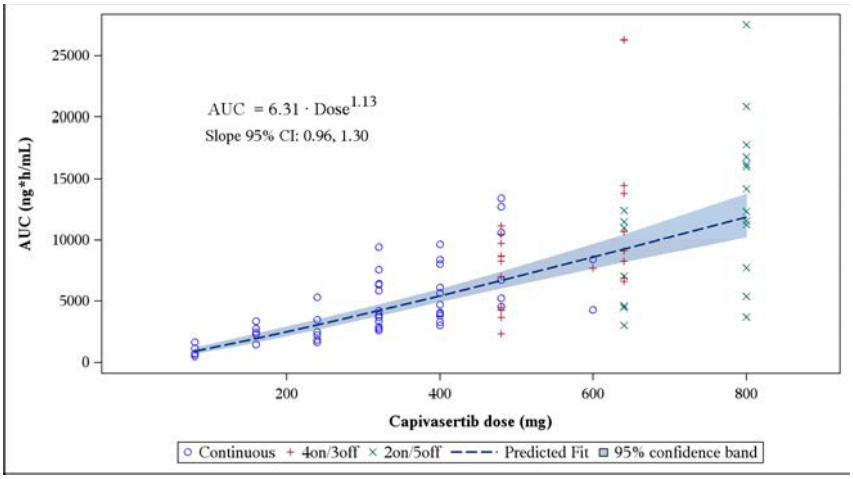
Capivasertib is primarily eliminated by metabolism.

Dose proportionality and time dependencies

Based on NCAs of data generated in FTHI study D3610C00001, capivasertib exposure (AUC and Cmax) is dose-proportional over the range 80 to 800 mg after single dose administration in patients. After multiple-dose administration of 80 to 600 mg BD continuously, the AUC increased slightly more than in proportion to the dose. See figures below:

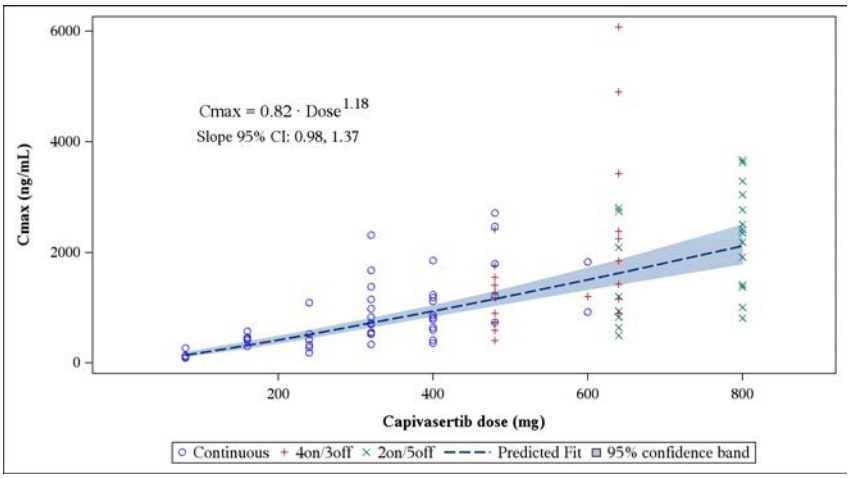
Figure 3 Capivasertib exposure versus dose following single-dose administration

AUC



Data from all schedules are included in the regression.

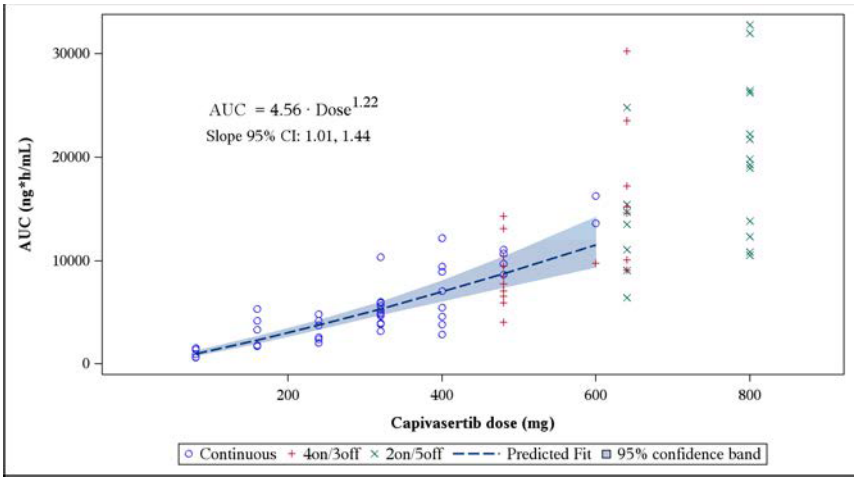
Cmax



Data from all schedules are included in the regression.

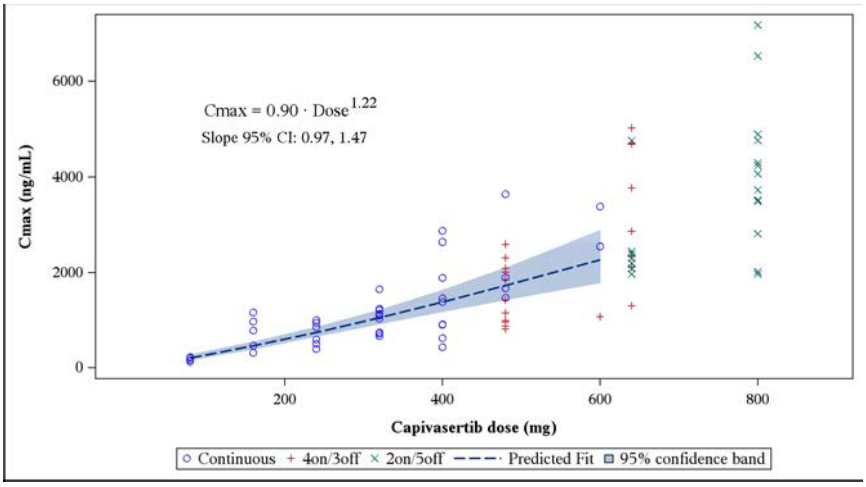
Figure 4 Capivasertib exposure versus dose following multiple-dose administration

AUC



Data from the intermittent schedules are shown for comparison but were not included in the regression.

Cmax



Data from the intermittent schedules are shown for comparison but were not included in the regression.

Special populations

Clinical pharmacology studies to specifically evaluate the role of impaired renal function, impaired hepatic function, age and gender have not been conducted. However, population PK analysis was performed using pooled data from of Phase I, II and III studies.

Impaired renal function

A formal clinical study to investigate the impact of renal impairment on the PK of capivasertib has not been performed. The justification provided by the applicant is based on the fact that capivasertib is only renally cleared to a small extent (renal clearance was 21% of total clearance in healthy subjects (in ADME study D361400007)) and only 3.8% to 7.4% of an oral dose was excreted unchanged in urine in patients (in FTIH study D3610C00001). In study D3610C00001, taking plasma protein binding of AZD5363 into account, renal clearance was high compared to the glomerular filtration rate indicating that renal excretion may have an active component.

The population PK analysis included patients with normal renal function at baseline (424 [54.3%] patients), mild renal impairment (267 [34.2%] patients), moderate renal impairment (85 [10.9%] patients), and patients with missing information (5 [0.6%] patients). Creatinine clearance did not have a significant effect on CL in the popPK analysis. Comparison of exposures revealed that the AUCss ratio was 1.01 (95% CI: 0.97, 1.06) and the Cmax,ss ratio was 1.01 (95% CI: 0.97, 1.05) in patients with mild renal impairment (creatinine clearance 51 to 80 mL/min) compared to patients with normal renal function. The AUCss ratio was 1.16 (95% CI: 1.08, 1.24) and the Cmax,ss ratio was 1.16 (95% CI: 1.09, 1.23) in patients with moderate renal impairment (creatinine clearance 31 to 50 mL/min) compared to patients with normal renal function. Based on these results, AUC and Cmax were 1% higher in patients with mild renal impairment (creatinine clearance 60 to 89 mL/min), compared to patients with normal renal function. AUC and Cmax were 16% higher in patients with moderate renal impairment (creatinine clearance 30 to 59 mL/min), compared to patients with normal renal function.

There is no data in severe renal impairment or end-stage renal disease (creatinine clearance < 30 ml/min).

Impaired hepatic function

A formal clinical study to investigate the impact of hepatic impairment on the PK of capivasertib has not been performed.

The population PK analysis included patients with normal hepatic function at baseline (505 [64.7%] patients), mild hepatic impairment (268 [34.3%] patients), moderate hepatic impairment (7 [0.9%] patients), and patients with missing information (1 [0.1%] patients). The analysis indicated that there was no statistically significant effect of hepatic impairment at baseline on the PK of capivasertib and that the estimated differences were small. The AUCss ratio was 1.05 (95% CI: 1.01, 1.10) and the Cmax,ss ratio was 1.05 (95% CI: 1.01, 1.09) in patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN, or bilirubin > 1 ULN to ≤ 1.5 ULN) compared to patients with normal hepatic function. The AUCss ratio was 1.17 (95% CI: 0.94, 1.47) and the Cmax,ss ratio was 1.13 (95% CI: 0.93, 1.36) in patients with moderate hepatic impairment (bilirubin > 1.5 ULN to ≤ 3 ULN), compared to patients with normal hepatic function.

Based on these results, AUC and Cmax were 5% higher in patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN, or bilirubin > 1 ULN to ≤ 1.5 ULN), compared to patients with normal hepatic function (bilirubin ≤ ULN and AST ≤ ULN). AUC was 17% and Cmax was 13% higher in patients with moderate hepatic impairment (bilirubin > 1.5 ULN to ≤ 3 ULN), compared to patients with normal hepatic function. There is limited data in patients with moderate hepatic impairment and no data in severe hepatic impairment.

Effect of race, age, gender and weight

Study D3610C00004 (A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Ascending Doses of AZD5363 under Adaptable Dosing Schedules in Japanese Patients with Advanced Solid Malignancies) was a Phase I, open label, multicentre study which was planned to consist of 2 parts: Part A (dose escalation) and Part B (dose expansion [optional, not conducted]). Plasma samples were collected pre-dose and up to 48 hours post-dose (single dose of capivasertib) and up to 12 hours post-dose (multiple doses of capivasertib) and an NCA to derive the PK parameters after single and multiple dosing of capivasertib was performed. The study results informed the pop pk analysis.

In the Japanese safety/PK study (D3610C00004), systemic exposure to capivasertib in Asian patients with advanced solid malignancies was similar to that in patients of White race with advanced solid malignancies in Part A and Part B of the FTIH study (D3610C00001): after repeated dosing, the dose-

normalised ratio (Asian/White) was 1.11 (90% CI: 0.96, 1.28) and 1.19 (90% CI: 1.01, 1.41) for AUC and Cmax, respectively (pooled data across doses).

The number of patients included in the pooled population PK analysis are presented by age category and study in the table below.

Table 22 Number of patients by age category and study

PK Trials	**Age 65-74 (Older subjects number /total number)**	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
D3610C00001	57/280	7/280	1/280
D3610C00002	18/90	1/90	0/90
D3610C00004	4/41	0/41	0/41
D3610C00007	8/30	2/30	0/30
D3615C00001	86/340	21/340	0/340
Total	173/781	31/781	1/781

Based on population pharmacokinetic analysis, AUC and Cmax showed that race (including White and Japanese patients), gender or age did not significantly impact the capivasertib exposure. There was a statistically significant correlation of apparent oral clearance of capivasertib to body weight. Compared to a patient with a body weight of 66 kg, a 47 kg patient is predicted to have 12% higher AUC. There is no basis for dose modification based on body weight as the predicted effect on capivasertib exposure was small.

No dose adjustment is required for elderly patients. There are limited data in patients aged ≥ 75 years.

Pharmacokinetic interaction studies

The effect of extrinsic factors on capivasertib PK was assessed *in vivo* in studies listed below:

Table 23 In vivo studies to assess the effect of extrinsic factors on capivasertib PK

Study identifier	Study population	Key design features	Study treatment	Status	Location in Module 5
Midazolam DDI study (D3614C00003)	Patients with advanced solid tumours	Phase I, open-label, fixed- sequence, multicentre study to assess the PK of midazolam when administered alone and in combination with repeated doses of capivasertib (N = 21 treated)	Part A: C1D1: single oral dose of midazolam (1 mg); C1D2 to C1D7: capivasertib 400 mg BD, 4 days on, 3 days off; C1D8 to C1D15: single oral doses of midazolam (1 mg, C1D8 and C1D12) during intermittent capivasertib treatment (400 mg BD, C1D9 to C1D12 on, C1D13 to C1D15 off) Part B: capivasertib 400 mg BD, 4 days on, 3 days off, as monotherapy or in combination with standard of care treatment, until disease progression or other discontinuation criteria are met.	Part A: Completed Part B: Ongoing	5.3.3.4
Itraconazole DDI study (D3614C00004)	Healthy subjects	Phase I, open-label, fixed sequence study in healthy subjects to assess the PK of capivasertib alone and in combination with itraconazole (N = 11 treated)	Capivasertib 80 mg single dose on Day 1 and Day 6 Itraconazole 200 mg BD on Day 3, followed by once daily doses in morning for 4 days	Completed	5.3.3.4
Food/PPI study (D3614C00005)	Healthy subjects	Phase I, open-label, randomised, crossover study in healthy subjects to evaluate the effect of food and acid- reducing agent(s) on the PK of capivasertib. 2-part study (adaptive design), each part 3-way crossover (Part 1: N = 23 treated + Part 2: N = 24 treated)	Capivasertib tablet, 3 single doses of 400 mg per part: Part 1: capivasertib overnight fasted, capivasertib after high-fat high-calorie meal, capivasertib fasted + rabeprazole. Part 2 (based on the findings of Part 1): capivasertib overnight fasted, capivasertib after low-fat low- calorie meal, capivasertib partially fasted; not administered: capivasertib + famotidine, capivasertib fed + rabeprazole.	Completed	5.3.3.4

Source: Excerpt 5.2 Tabular Listing of All Clinical Studies

Results from published clinical studies by "Kolinsky et al. 2020[1]" and "Jones et al. 2020[2]" have also been discussed.

[1] Kolinsk et al.; A phase I dose-escalation study of enzalutamide in combination with the AKT inhibitor AZD5363 (capivasertib) in patients with metastatic castration-resistant prostate cancer; Ann Oncol 2020;31:619-625
[2] R H Jones et al.; Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial; Vol Lancet Oncology 2020:21:345-357

Table 24 Summary statistics for midazolam PK parameters with and without capivasertib

Parameter (unit)	Summary	C1D1 [N = 21]	C1D8 [N = 19]	C1D12 [N = 18]
AUCinf (h*ng/mL)	gMean	22.95 [n = 15]	26.08 [n = 14]	39.31 [n = 14]
	gCV%	55.56	45.98	36.65
AUClast (h*ng/mL)	gMean	21.27 [n=15]	23.07 [n=14]	34.44 [n=14]
	gCV%	51.89	43.04	33.64
Cmax (ng/mL)	gMean	8.002 [n=15]	9.016 [n=14]	9.673 [n=14]
	gCV%	35.74	47.31	40.62
t½λz (h)	gMean	6.740 [n = 15]	7.980 [n = 14]	7.203 [n = 14]
	gCV%	28.67	63.06	39.78
tmax (h)	Median	0.53 [n = 15]	0.47 [n = 14]	0.55 [n = 14]
	Min, Max	0.25 - 0.90	0.18 - 0.75	0.25 - 1.08

C1D1: Day 1 of Cycle 1; single oral dose of midazolam (1 mg).
C1D8: Day 8 of Cycle 1; single oral dose of midazolam (1 mg) on 3rd off day of intermittent capivasertib treatment (400 mg bid).
C1D12: Day 12 of Cycle 1; single oral dose of midazolam (1 mg) on 4th on day of intermittent capivasertib treatment (400 mg bid).
AUCinf = Maximum observed plasma (peak) drug concentration; AUClast = Area under the plasma concentration-time curve from zero to last observed timepoint; bid = twice daily; C = Cycle; Cmax = Maximum observed plasma (peak) drug concentration; CV% = Coefficient of variation; D = Day; gCV% = Geometric coefficient of variation; n = number of observations in analysis; N = number of patients per visit; t½λz = Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve; tmax = Time to reach maximum observed (peak) plasma concentration.

Capivasertib effect on other drugs (capivasertib=perpetrator)

CYP inhibition (capivasertib=perpetrator)

Study D3614C00003 (An Open-label, Fixed-sequence Study to Assess the Effect of Repeated Doses of Capivasertib on the Pharmacokinetics of Oral Midazolam (a CYP450 3A Probe) in Patients with Advanced Solid Tumours) is an ongoing Phase I open-label, fixed-sequence, multicentre study to assess the pharmacokinetics (PK) of midazolam when administered alone and in combination with repeated doses of capivasertib in patients with advanced solid tumours and who may be suitable for capivasertib treatment.

Table 25 Statistical comparison of key PK parameters for midazolam (PK analysis set)

Parameter (unit)	Time point	n	LS mean	95% CI	Comparison of treatments		
					Comparison	Geometric mean ratio (%)	90% CI
AUCinf (h*ng/mL)	C1D1 N = 15	15	22.95	(18.08, 29.13)	NA	NA	NA
	C1D8	14	26.29	(20.63, 33.49)	C1D8 vs C1D1	114.5	(96.53, 135.9)

	N = 13						
	C1D12 N = 14	14	40.67	(31.93, 51.82)	C1D12 vs C1D1	177.2	(149.4, 210.3)
Cmax (ng/mL)	C1D1 N = 15	15	8.002	(6.476, 9.887)	NA	NA	NA
	C1D8 N = 13	14	8.938	(7.205, 11.09)	C1D8 vs C1D1	111.7	(94.75, 131.7)
	C1D12 N = 14	14	9.928	(8.003, 12.31)	C1D12 vs C1D1	124.1	(105.2, 146.3)

C1D1: Day 1 of Cycle 1; single oral dose of midazolam (1 mg).
C1D8: Day 8 of Cycle 1; single oral dose of midazolam (1 mg) on 3rd off day of intermittent capivasertib treatment (400 mg bid).
C1D12: Day 12 of Cycle 1; single oral dose of midazolam (1 mg) on 4th on day of intermittent capivasertib treatment (400 mg bid).
Results based on mixed effects model following a natural logarithmic transformation of the PK parameters with fixed effect for day and random effect for patient.
CI = Confidence interval; LS = least-squares; n = number of patients in analysis; N = number of patients per visit.AUCinf = Maximum observed plasma (peak) drug concentration; C = Cycle; Cmax = Maximum observed plasma (peak) drug concentration; D= Day; n = number of observations in analysis; N = number of patients per visit; NA = not applicable; PK = pharmacokinetic(s).

Transporter (capivasertib=perpetrator)

The potential of capivasertib to interact with transporters has not been investigated in clinical studies.

Effect of other drugs on capivasertib (capivasertib=victim)

CYP3A4 inhibitors (capivasertib=victim)

Study D3614C00004 was an "Open-label, Fixed Sequence Study in Healthy Subjects to Assess the Pharmacokinetics of Capivasertib When Administered Alone and In Combination with Itraconazole".

Table 26 Summary statistics for capivasertib PK parameters with and without itraconazole

Parameter (Unit)	Summary	Capivasertib	
		Period 1 (N=11) without concomitant itraconazole	Period 3 (N=11) with concomitant itraconazole
Cmax (ng/mL)	gMean	121.1	206.0
	(gCV%)	(34.62)	(31.46)
AUCinf (h*ng/mL)	gMean	597.6	1167
	(gCV%)	(26.92)	(21.92)
AUClast (h*ng/mL)	gMean	573.8	1135
	(gCV%)	(28.52)	(21.56)
tmax (h)	Median	1.50	1.50
	(Min, Max)	(0.50-3.50)	(0.50-2.52)
t1/2λz (h)	Mean	7.390	10.28
	(SD)	(1.383)	(1.105)
tlast (h)	Median	24.05	47.95
	(Min, Max)	(23.97-47.52)	(47.78-48.07)
CL/F (L/h)	gMean	133.9	68.57
	(gCV%)	(26.92)	(21.92)
Vz/F (L)	gMean	1407	1012
	(gCV%)	(22.44)	(21.09)
M:P [AUCinf]	gMean	NA	NA
	(gCV%)	(NC)	(NC)

Period 1 = 80 mg capivasertib; Period 3 = 80 mg capivasertib and 200 mg itraconazole
gCV% = geometric coefficient of variation; gMean = geometric mean; Max = maximum; min = minimum; NA = Not applicable; NC = Not calculated; M:P = ratio of metabolite

Table 27 Statistical comparison of key PK parameters: DDI assessment (PK set)

			n	Geometric mean	95% CI	Pairwise comparisons		
						Pair	Ratio of LS geometric means (%)	90% CI
Cmax (ng/mL)	A	11		121.1	(97.88, 149.8)			
	C	11	11	206.0	(166.5, 254.9)	C/A	170.1	(155.6, 186.0)
AUCinf (h*ng/mL)	A	11		597.6	(509.5, 701.0)			
	C	11	11	1167	(994.6, 1368)	C/A	195.2	(181.8, 209.6)
AUClast (h*ng/mL)	A	11		573.8	(487.1, 676.0)			
	C	11	11	1135	(963.2, 1337)	C/A	197.7	(183.3, 213.3)

Treatment A = Period 1, 80 mg capivasertib; Treatment C = Period 3, 80 mg capivasertib and 200 mg itraconazole

CYP3A4 inducers (capivasertib=victim)

Study results of the RE-AKT study have been published by M. P. Kolinsky et al.[3]. As summarised by the applicant, the RE-AKT study comprised a Phase I safety run-in, followed by a randomised Phase II study of capivasertib + enzalutamide versus placebo + enzalutamide, with a Phase II expansion cohort of capivasertib + enzalutamide, in patients with metastatic Castration-Resistant Prostate Cancer (mCRPC).

The effect of enzalutamide on the PK of capivasertib was assessed as a secondary objective. Patients in all parts of the study received enzalutamide 160 mg OD. Capivasertib was administered 4 days on, 3 days off at doses of 320, 400, or 480 mg BD in the safety run-in, and at 400 mg BD in the Phase II parts.

Capivasertib AUC was 40% lower on Cycle 2, Day 1 (capivasertib + enzalutamide) than on Cycle 0, Day 1 (capivasertib) (GMR for AUC of 0.60).

After accounting for the predicted accumulation between Cycle 0 Day 1 and Cycle 2 Day 1 (ratio 1.08) based on the population PK model, the estimated decrease in capivasertib AUC by enzalutamide is approximately 40% to 50%.

Inhibitors/inducers of UGT2B7 (capivasertib=victim)

The potential of DDIs based on interactions with UGT2B7 (capivasertib as a victim) have not been investigated in clinical studies.

Inhibitors of transporters (capivasertib=victim)

The potential of DDIs based on interactions of inhibitors of transporters (capivasertib as a victim) have not been investigated in clinical studies.

Antacids, H2 antagonists, and proton pump inhibitors (PPI)

Study D3614C00005 was a Phase I, 2-part, adaptive, open-label, randomised, crossover study to evaluate the effect of food and acid-reducing agents on the PK of capivasertib in healthy subjects.

[3] Kolinsk et al.; A phase I dose-escalation study of enzalutamide in combination with the AKT inhibitor AZD5363 (capivasertib) in patients with metastatic castration-resistant prostate cancer; Ann Oncol 2020;31:619-625

Table 28 Statistical comparison of key pharmacokinetic parameters - Part 1 (pharmacokinetic analysis set)

					Comparison of treatment groups	
Parameter[a]	Treatment Comparison	n	Geometric LS mean	95% CI	GMR	GMR 90% CI
Cmax (ng/mL)	B versus A	22 vs 22	757.1 vs 614.0	(671.1, 854.1) vs (544.4, 692.6)	1.233	(1.078, 1.410)
	C versus A	21 vs 22	449.7 vs 614.0	(397.6, 508.5) vs (544.4, 692.6)	**0.7323**	**(0.6393, 0.8389)**
AUCinf (h*ng/mL)	B versus A	22 vs 22	4341 vs 3282	(3932, 4793) vs (2973, 3623)	1.323	(1.223, 1.431)
	C versus A	21 vs 22	3078 vs 3282	(2784, 3402) vs (2973, 3623)	**0.9378**	**(0.8658, 1.016)**
AUClast (h*ng/mL)	B versus A	22 vs 22	4250 vs 3203	(3851, 4689) vs (2903, 3534)	1.327	(1.226, 1.436)
	C versus A	21 vs 22	2984 vs 3203	(2701, 3297) vs (2903, 3534)	**0.9316**	**(0.8597, 1.010)**

a For definitions of pharmacokinetic parameters see Section 4.
CI Confidence interval; GMR Geometric mean ratio; LS Least-squares; n Number of subjects in analysis.
Treatment A:** Single oral dose of 400 mg capivasertib, fasted state **(reference treatment).
Treatment B: Single oral dose of 400 mg capivasertib, fed state (after a high-fat, high-calorie meal).
***Treatment C:** Twice daily oral doses of **20 mg rabeprazole for 3 days** (Days -3 to -1) and a single dose on the morning of Day 1 + a single oral dose of 400 mg capivasertib under fasted conditions on Day 1.*
Result based on a mixed effects model of log transformed PK parameter with treatment, sequence, period as fixed effects and subject within sequence as random effect. Geometric LS mean and corresponding 95% CI are back-transformed. Geometric mean ratio and corresponding CI are back-transformed. Treatment comparison B vs A and C vs A refers to Treatment A as the reference and thus the GMR refers to the ratio B/A and C/A respectively.

Interaction of capivasertib and fulvestrant (capivasertib=victim or perpetrator)

In a publication by Jones et al.[4] cited by the applicant, a comparison of trough fulvestrant concentrations between the capivasertib + fulvestrant arm and the placebo + fulvestrant arm in the FAKTION study in patients with advanced HR+/HER2- breast cancer showed no relevant effect of capivasertib on the plasma levels of fulvestrant.

[4] R H Jones et al.; Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial; Vol Lancet Oncology 2020:21:345-357

Table 29 FAKTION: PK analysis of mean minimum fulvestrant concentration

Cycle and Day	Placebo				Capivasertib			
	Geometric mean Cmin	95% CI (Geometric mean Cmin)		n	Geometric mean Cmin	95% CI (Geometric mean Cmin)		n
C1 D15	9.64	8.87	10.46	60	9.47	8.54	10.49	56
C2 D1	13.26	12.08	14.48	57	14.57	13.34	15.92	56
C3 D1	10.34	9.60	11.13	48	10.46	9.63	11.36	46

Source: Table 5 of Jones et al 2020 (supplementary information) taken from the submitted CS 2.7.2

In the FTIH study (D3610C00001), no effect of fulvestrant on the plasma levels of capivasertib was observed (Parts E and F). Plasma levels of capivasertib following the administration of capivasertib + fulvestrant were similar to those after administration of capivasertib monotherapy.

Table 30 FTIH Study (D3610C00001): Dose-normalised (to 400 mg) capivasertib plasma concentrations in patients with (parts E and F) and without (parts C and D) concomitant fulvestrant

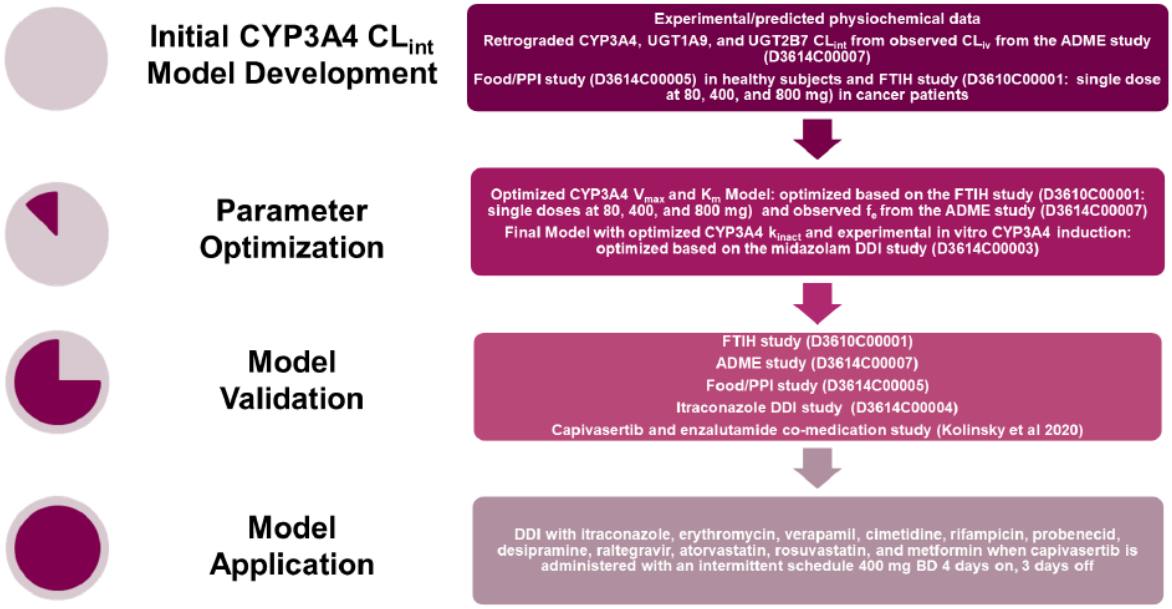
Concentration (ng/mL)	Pre-dose		2 hours		4 hours	
Study parts[a]	C and D[b]	E and F[c]	C and D[b]	E and F[c]	C and D[b]	E and F[c]
N	103	59	100	56	100	55
Geometric mean	272	249	1085	1270	773	835
95% CI	238, 309	207, 301	942, 1250	1119, 1441	678, 883	732, 952

[a] FTIH Study (D3610C00001) Visit 5 (Day 11).
[b] Parts C and D: capivasertib 480 mg without concomitant fulvestrant.
[c] Parts E and F: capivasertib 400 mg with concomitant fulvestrant.

In the population PK analysis, in patients treated with concomitant fulvestrant, the ratios for AUCss and Cmax,ss were 1.05 (95% CI: 1.01, 1.09) and 1.06 (95% CI: 1.02, 1.10) compared to patients who did not receive concomitant fulvestrant. These results indicate that fulvestrant has no relevant impact on the PK of capivasertib.

A PBPK model for capivasertib was developed based on internally generated physicochemical data and the clinical studies of capivasertib alone after single dose oral or intravenous administration in healthy subjects (food/PPI study (D3614C00005) and ADME study (D3614C00007)) and/or cancer patients (FTIH study (D3610C00001)). The CYP3A4 Km and Vmax of capivasertib were optimised using the clinical PK data of capivasertib after single dose of 80, 400, and 800 mg oral administration in cancer patients in the FTIH study (D3610C00001) and renal excretion data in healthy subjects in the ADME study (D3614C00007). Also, the k_{inact} for CYP3A4 time-dependent inhibition of capivasertib was optimised to match with the observed clinical DDI between midazolam and capivasertib in the midazolam DDI study (D3614C00003). The advanced dissolution, absorption and metabolism (ADAM) model, which describes the drug absorption from each gut segment as a function of dissolution, precipitation, luminal degradation, permeability, metabolism, transport, and transit from one segment to another, was utilised to describe capivasertib oral absorption. A full PBPK model assuming all tissues/organs as perfusion limited compartments was applied.

Figure 5 Modelling workflow overview



ADME Absorption, metabolism, distribution, and excretion; CL_{int} Intrinsic clearance; CL_{iv} Intravenous clearance; DDI Drug-drug interaction; f_e Fraction of renal excretion; K_m Michaelis constant; V_{max} Maximum rate of metabolism.

According to the applicant, the developed model was validated using the clinical studies of capivasertib alone after single or multiple dose administration in cancer patients in the FTIH study (D3610C00001) or in healthy subjects in the food/PPI study (D3614C00005) and ADME study (D3614C00007). The itraconazole DDI study (D3614C00004) was used to validate the fraction of metabolism by CYP3A4. In addition, the model was validated with a study in which capivasertib was combined with a strong CYP3A4 inducer, enzalutamide (Kolinsky et al 2020), to confirm capivasertib's drug interaction potential as a CYP3A4 substrate. Finally, the validated PBPK model was applied to predict the potential impact of coadministration of capivasertib at intermittent dosing schedule with other CYP3A4 inhibitors (erythromycin, verapamil, and cimetidine), CYP3A4 inducer (rifampicin), sensitive CYP2D6 substrate (desipramine), UGT1A1 substrate (raltegravir), and transporter substrates (atorvastatin (for OATP1B1), rosuvastatin (for OATP1B1 and OATP1B3 and BCRP), and metformin (for MATE1 and OCT2)).

Pharmacokinetics using human biomaterials

Metabolic profiling in plasma and urine of patients and reaction phenotyping

Study DMPKTrax_079 quantified metabolites of capivasertib in human plasma using NMR spectroscopy and characterised capivasertib metabolites in plasma and urine with UHPLC-UV-MS. The samples used were from the first-in-human multiple-ascending-dose (MAD) study D3610C00001. NMR analysis detected two plasma metabolites, ether glucuronide M2 present at 82.7% of total parent-related material, and a minor metabolite (+ 3[O], M1) at 1.9% of total parent-related material. The only other quantifiable substance was capivasertib itself, present at 15.4% of total circulating parent-related material. The complementary UHPLC-UV data were in line with these findings showing the two metabolites (M2, M1) and capivasertib present at 78.0, 1.2 and 17.0% of total parent-related material, respectively.

Study BE002560-11 used the original LC-UV-MS data from study DMPKTrax_079 to reveal that the quantity of M2 (ether glucuronide metabolite of capivasertib) in human urine was 4.9-fold higher than the parent compound (83 vs. 17%, respectively).

Interplay of transport and metabolism in human hepatocytes

In vitro concentration-time profiles of capivasertib in absence and presence of rifamycin SV (OATP inhibitor) and 1-aminobenzotriazole (broad range CYP inhibitor) were analysed in study BE000901-57. The results showed that the contribution of active transport comprises 45% of the total uptake of capivasertib in human hepatocytes *in vitro*. In this system, the unbound intracellular concentration of the compound was 1.8-fold higher compared to that in the extracellular medium.

Potential for drug interactions: in vitro studies with metabolic enzymes

In vitro studies assessing possible relevance of CYP (cytochrome P450) and UGT (UDP-glucuronosyltransferase) enzymes for drug interactions of capivasertib are summarised in the table below. Studies for the ether glucuronide AZ14102143 are summarised in the table thereafter.

Table 31 Overview of in vitro studies assessing relevance of metabolic enzymes for drug interactions of capivasertib

Study nr.	Capivasertib:	Study system	Enzymes / Receptors	Results / unbound IC_{50} or K_i	Implications
AZM100108-02	activator	PXR-transfectedHepG2 cells	PXR	50 μM: no activation	-
301078331 (KMX018)	inducer	human hepatocytes NB: 64-86% viability at 5 and 15 μM	CYP1A2	↑mRNA not dose-dep. <2× at 15×$C_{max,u}$ ↑activity dose-dep. <2× at 15×$C_{max,u}$	*in vivo* relevance unlikely*
			CYP2B6	↓activity dose-dep. only in 1/3 donors	
			CYP3A4	↑mRNA dose-dep. >2× at 15×$C_{max,u}$	*in vivo* relevance likely*
ONC5363-0001PK_CYP	inducer	human hepatocytes RIS-qualified donor	CYP3A4	↑mRNA dose-dep. RIS = 0.349 R_3 = 0.274	*in vivo* relevance likely**
BS001265-62	inhibitor	human liver microsomes	UGT1A1	IC_{50} = 84.9 μM	*in vivo* study warranted***
			UGT2B7	IC_{50} > 300 μM	no *in vivo* study needed***
BS001705-69	inhibitor	human liver microsomes	UGT1A9	1 mM: no inhibition	no *in vivo* study needed***
BS003400-56	inhibitor	human liver microsomes	UGT1A4	300 μM: 45.5% inhibition (IC_{50} 300 μM assumed)	clinical DDI cannot be excluded***
KMX009	inhibitor	human liver microsomes	CYP1A2	50 μM: no inhibition	further studies needed
			CYP2A6	50 μM: no inhibition	
			CYP2B6	50 μM: 58.4% inhibition	
			CYP2C8	50 μM: no inhibition	
			CYP2C9	IC_{50} > 16.7 μM	
			CYP2C19	50 μM: 67.0% inhibition	
			CYP2E1	50 μM: no inhibition	
			CYP2D6	K_i = 2.7 μM	*in vivo* study warranted***
			CYP3A4/5	IC_{50} > 16.7 μM TDI	further studies needed
BS001265-84	inhibitor	human liver microsomes	CYP2A6	150 μM: no inhibition	no *in vivo* study needed***
			CYP2B6	IC_{50} = 134 μM	
			CYP2C8	IC_{50} > 150 μM	
			CYP2E1	IC_{50} > 150 μM	
			CYP3A4 (nifedipine)	IC_{50} > 150 μM	
BS001265-85	inhibitor	human liver microsomes	CYP1A2	150 μM: no inhibition	no *in vivo* study needed***
			CYP2C9	IC_{50} = 75.7 μM	clinical DDI cannot be excluded***
			CYP2C19	IC_{50} ~ 119-125 μM	no *in vivo* study needed***
			CYP2D6	IC_{50} = 15.2 μM	

			CYP3A4/5 (midazolam)	IC_{50} = 54.7 μM	*in vivo* study warranted***
KMX004	inhibitor, TDI	human liver microsomes	CYP3A4/5	k_{inact} = 0.040 1/min K_i = 10.5 μM	time-dependent inhibitor
KMX014	inhibitor, TDI	human hepatocytes	CYP3A4/5	k_{inact} = 0.027 1/min K_i = 24 μM	time-dependent inhibitor

Need for *in vivo* study as estimated by the assessor according to the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**) and draft ICH M12 guideline on drug interactions:
in vivo evaluation is warranted if
* at least in one donor a drug increases mRNA expression of a CYP enzyme in a concentration-dependent manner and the fold-change of CYP mRNA expression is ≥ 2-fold at $15\times_{Cmax,u}$,
** RIS / R < 0.8,
***[I]/Ki ≥ 0.02 where [I] is the unbound mean Cmax obtained during treatment with the highest recommended dose ([I] = 0.717 μM), for intestinal enzymes [I]/Ki ≥ 10 where [I] is max. dose taken one occasion/ 250 ml, Ki is estimated as $IC_{50}/2$

Table 32 Overview of in vitro studies assessing relevance of metabolic enzymes for drug interactions of AZ14102143

Study nr.	AZ14102143:	Study system	Enzymes / Receptors	Results / IC_{50} or K_i	Implications
BS001884-52	inhibitor	human liver microsomes	CYP2A6	300 μM: 10.2% inhibition	inconclusive*
			CYP2B6	300 μM: 18.2% inhibition	
			CYP2C8	300 μM: no inhibition	
			CYP2E1	300 μM: 11.4% inhibition	
			CYP3A4/5 (nifedipine)	300 μM: no inhibition	
BS001884-58	inhibitor	human liver microsomes	CYP1A2	300 μM: 22% inhibition	inconclusive*
			CYP2C9	300 μM: no inhibition	
			CYP2C19	300 μM: 13.1% inhibition	
			CYP2D6	300 μM: 9.13% inhibition	
			CYP3A4/5 (midazolam)	300 μM: no inhibition	
BS004445-50	inhibitor	human liver microsomes	UGT1A1	IC_{50} = 843 μM	no *in vivo* study needed*
			UGT2B7	1 mM: no inhibition	
BS004445-51	inhibitor	human liver microsomes	CYP1A2	IC_{50} = 898 μM	no *in vivo* study needed*
			CYP2C9	1 mM: no inhibition	
			CYP2C19	1 mM: 19.2% inhibition	
			CYP2D6	1 mM: 35.3% inhibition	
			CYP3A4	1 mM: 23.9% inhibition	
BS004445-52	inhibitor	human liver microsomes	CYP2A6	1 mM: 12.1% inhibition	no *in vivo* study needed*
			CYP2B6	1 mM: 49.5% inhibition	
			CYP2C8	1 mM: 19.1% inhibition	
			CYP2E1	IC_{50} = 193 μM	*in vivo* study warranted* but not needed due to lack of clinically relevant substrates
			CYP3A4	1 mM: 31.6% inhibition	

*Need for *in vivo* study as estimated by the assessor according to the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**) and draft ICH M12 guideline on drug interactions: in vivo evaluation is warranted if
$[I]/K_i \geq 0.02$ where [I] is the unbound mean C_{max} obtained during treatment with the highest recommended dose ([I] = 18.54 × 0.368 = 6.82 μM)

Potential for drug interactions: in vitro studies with transporters

In vitro studies assessing possible relevance of transport proteins for drug interactions of capivasertib are summarised in the table below. The results for the metabolite AZ14102143 are presented in the table thereafter.

Table 33 Overview of in vitro studies assessing relevance of transporters for drug interactions of capivasertib

Study nr.	Capivasertib:	Study system	Transporters	Results / unbound IC_{50} or K_i	Implications
19AZTrP7	substrate	HEK293 cells overexpressing transporters	OATP1B1	efflux ratio OATP1B cells vs. ctrl < 2 =with inhibitor	not a transporter substrate
			OATP1B3		
BE000458-19	inhibitor	Caco-2 cells	BCRP	IC_{50} = 100.1 μM	*in vivo* study warranted*
Pgp_inhib	inhibitor	MDCKII-MDR1 cells	P-gp	no inhibition up to 300 μM	no *in vivo* study needed*
05102012	inhibitor	HEK293 cells overexpressing OATP1B1	OATP1B1	IC_{50} = 15 μM	*in vivo* study warranted*
16AZTrP3	substrate	MDCK cells overexpressing transporters	P-gp	efflux ratio MDR1 cells vs. ctrl > 2 ↓with inhibitor	transporter substrate
			BCRP	efflux ratio BCRP cells vs. ctrl < 2 =with inhibitor	not a transporter substrate
	inhibitor	HEK293 cells overexpressing transporters	MATE1	IC_{50} = 1.79 μM	*in vivo* study warranted*
			MATE2-K	IC_{50} = 14.0 μM	*in vivo* study warranted*
			OATP1B3	IC_{50} = 25.2 μM	*in vivo* study warranted*
			OAT1	13.9% inhibition at 100 μM	no *in vivo* study needed*
			OAT3	↑uptake at <10 μM IC_{50} ~ 28 μM	
KMN025	inhibitor	HEK293 cells overexpressing OCT2	OCT2	IC_{50} = 1.34 μM	*in vivo* study warranted*
	substrate			uptake ratio OCT2 cells vs. ctrl < 2 + inhibitor ↓22%	minor OCT2-mediated uptake

**need for *in vivo* study as estimated by the assessor according to the ICH M12 draft guideline on drug interactions: *in vivo* evaluation is warranted if K_i ≤
- for BCRP and P-gp: 0.1-fold the maximum dose on one occasion/250 ml
- for OATP1B1 and OATP1B3: 10-fold the unbound hepatic inlet concentration (9.888 μM)
- for OCT2, OAT1 and OAT3: 10-fold unbound C_{max} (0.717 μM)
- for MATE1 and MATE2-K: 50-fold unbound C_{max} (0.717 μM)

Table 34 Overview of in vitro studies assessing relevance of transporters for drug interactions of AZ14102143.

Study nr.	AZ14102143:	Study system	Transporters	Results / unbound IC_{50} or K_i	Implications
BS001884-49	inhibitor	MDCKII-MDR1 cells	P-gp	no inhibition up to 300 μM	no *in vivo* study needed*
BS001884-49	inhibitor	Caco-2 cells	BCRP	no inhibition up to 300 μM	no *in vivo* study needed*
BS001884-51	inhibitor	HEK293 cells overexpressing OATP1B1	OATP1B1	IC_{50} = 65.8 μM	*in vivo* study warranted*
BS004445-53	inhibitor	MDCKII-MDR1 cells	P-gp	20% inhibition at 1 mM	no *in vivo* study needed*
BS004445-54	inhibitor	Caco-2 cells	BCRP	IC_{50} = 613 μM $IC_{50} \approx K_i$	no *in vivo* study needed*

*need for *in vivo* study as estimated by the assessor according to the ICH M12 draft guideline on drug interactions: in vivo evaluation is warranted if $K_i \leq$
- for BCRP and P-gp: 0.1-fold the maximum dose on one occasion/250 ml
- for OATP1B1: 10-fold the unbound hepatic inlet concentration (6.845 μM)

2.6.2.2. Pharmacodynamics

Mechanism of action

Capivasertib is a potent, selective inhibitor of the kinase activity of all 3 isoforms of serine/threonine kinase AKT (AKT1, AKT2 and AKT3). AKT is a pivotal node in the phosphatidylinositol 3-kinase (PI3K) signalling cascade regulating multiple cellular processes including cellular survival, proliferation, cell cycle, metabolism, gene transcription and cell migration. AKT activation in tumours is a result of upstream activation from other signalling pathways, mutations of AKT, loss of phosphatase and tensin homolog (PTEN) function and mutations in the catalytic subunit of PI3K (PIK3CA).

Capivasertib inhibits the phosphorylation of AKT substrates such as glycogen synthase kinase 3-β (GSK3β) and proline rich AKT substrate of 40 kilodaltons (PRAS40). Capivasertib reduces growth of a range of cell lines derived from solid tumours and haematological disease. Multiple breast cancer cell lines were sensitive to capivasertib monotherapy. Within cell lines showing greater sensitivity to capivasertib there was an enrichment of PIK3CA or AKT1 mutations, or loss of PTEN. Some cell lines lacking such mutations were also sensitive to capivasertib.

In vivo, monotherapy, capivasertib inhibits growth of human cancer xenograft models representative of different tumour types including ER+ and triple negative breast cancer models with PIK3CA, AKT1 mutations, PTEN loss and HER2 amplification, mutant xenograft models and triple negative breast cancer xenograft models. Combined treatment with capivasertib and fulvestrant demonstrated a greater anti-tumour response in a range of human breast cancer PDX models representative of different breast cancer subsets. This included models without detectable mutations or alterations in PIK3CA, PTEN or AKT, as well as models with mutations or alterations in PIK3CA, PTEN or AKT.

Primary and secondary pharmacology

Primary Pharmacology

FTIH study D3610C00001

Optional paired biopsies were collected and analysed for phospho-proline-rich serine/threonine specific protein kinase (AKT) substrate of 40 kilo Daltons (pPRAS40), phospho-glycogen synthase kinase-3-beta (pGSK3β), phospho-AKT (pAKT), phosphatidylethanolamine bonding protein 1 (pEBP1) and Foxo3a nuclear translocation.

- **Platelet rich plasma**

pGSK3β / pPRAS40

The mean percentage decrease from baseline in phosphorylation of PRAS40 ranged from 9% to 34%, one hour to12 hours after a single 80 mg to 800 mg dose of AZD5363. The maximal mean decrease of pPRAS40 at the Phase II RD (480 mg), was 33.9% four hours after a single dose of 480 mg AZD5363, and was 28.4% at steady state (C1D8, continuous dosing) and 31.0% at steady state (C4D1, intermittent dosing). The mean percentage decrease from baseline in phosphorylation of GSK3β ranged from 6% to 47%, four hours after a single 80 mg to 800 mg AZD5363. The maximal mean decrease of pGSK3β at the Phase II RD (480 mg) was 36.1% four hours after dosing a single dose of 480 mg AZD5363, and was 37.3% at steady state (C1D8, continuous dosing), and 23.9% at steady state (C4D1, intermittent dosing). In summary, there was a slight trend towards reduced pGSK3b with increasing AZD5363 concentrations observed, as was a slight trend towards reduced pPRAS40 with increasing AZD5363 concentrations. Although a reduction of pGSK3β and pPRAS40 was the expected response to the pharmacological activity of AZD5363, increased phosphorylation of these substrates compared to baseline was observed at some time points at all doses. These increases showed no consistent relationship with dose or time after dosing and was discussed to be most likely attributable to assay variability.

pAKT

The phosphorylation status of AKT Ser473 was generally increased in response to AZD5363. The maximum mean percentage increase from baseline in pAKT occurred within the first 24 hours after a single dose, and the maximum mean increase in pAKT after a single 80 mg to 800 mg dose of AZD5363 was 185%. Generally, the mean percentage increase from baseline for pAKT at steady state was larger than that achieved after a single dose. However, there was a mean percentage decrease from baseline in pAKT after both single dose and at steady state in the 480 mg bd (continuous) cohort. Also, at 600 mg bd (continuous) and 640 mg bd intermittent 2 on/5 off doses, the mean percentage increase from baseline in pAKT was lower at steady state than that observed after a single dose. In summary, the expected increase in pAKT change from baseline with increasing AZD5363 concentrations was not apparent in the platelet rich plasma data:

- **Plasma glucose levels**

The PDc activity of AZD5363 was supported by the observed increase in plasma glucose levels, which can be attributed to the role of AKT in the physiological regulation of glucose transport and uptake.

In summary, it was concluded that PD data indicated AZD5363 exerting a biologically relevant effect both on target and downstream of the target at the recommended dose.

Banerji et al. 2018

Combined data for paired tumour biopsies were collected from patients with advanced solid malignancies across a range of capivasertib doses and schedules following at least 7 days of treatment in the FTIH study (D3610C00001) and the Japanese safety/PK study (D3610C00004).

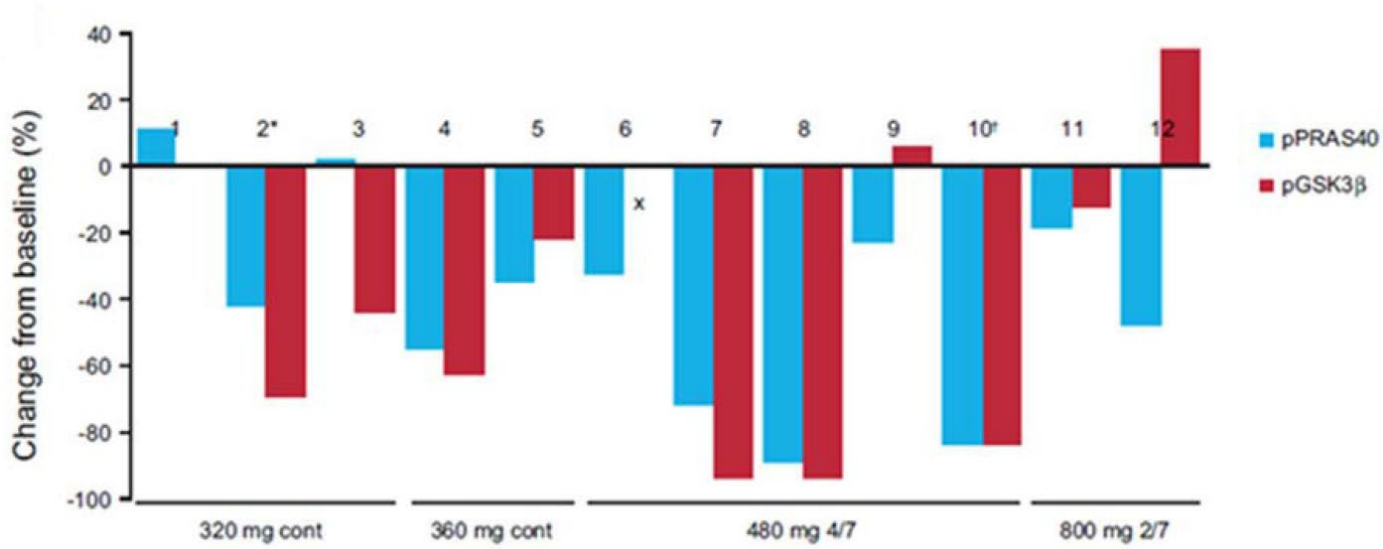
Data from these studies demonstrate inhibition of AKT after administration of capivasertib. Paired tumour biopsies from 12 patients with advanced solid malignancies (9 from the FTIH study [D3610C00001: Parts

A to C] and 3 from the Japanese safety/PK study [D3610C00004]) receiving a range of doses and schedules were evaluated to assess target engagement.

Changes in AKT pathway effectors, including pAKT, pPRAS40, pGSK3β and FOXO1/3a nuclear staining, were assessed using immunohistochemistry (IHC). Preclinical PK, PD and efficacy data were used to define "proof of mechanism (PoM) thresholds" for modulation in phosphorylation of the proximal biomarkers pPRAS40 and pGSK3β to provide confidence that on-target PoM was achieved: a greater than 50% inhibition in mean pPRAS40 or a greater than 30% inhibition in mean pGSK3β.

After treatment with capivasertib, downregulation of PD biomarkers was observed following at least 7 days of treatment. Greater than 50% inhibition of pPRAS40 was observed in 4 of 12 paired biopsies, with greater than 30% decrease in pGSK3β in 6 of 11 paired biopsies. Four of 11 samples met both endpoints, see figure below.

Figure 6 FTIH study (D3610C00001) part A and Japanese safety/PK study (D3610C00004): Effect on pGSK3β and pPRAS40 H scores from paired tumour biopsies



Cont = Continuous; 4/7 = 4 days on, 3 days off; 2/7 = 2 days on, 5 days off.
Percentage change is based on the average H score for individual biomarkers in baseline and on-treatment biopsies from 3 non-consecutive tissue sections. Each pair of bars represents data from an individual patient. X indicates missing data.
Tumour types: 1: clear-cell renal carcinoma; 2: colorectal adenocarcinoma (KRAS-mutant colorectal cancer); 3: hypopharyngeal cancer; 4: breast cancer; 5: mesothelioma; 6: mesothelioma; 7: colorectal adenocarcinoma; 8: medullary thyroid cancer; 9: liver metastasis from colorectal adenocarcinoma; 10: adenosquamous cervical carcinoma (PIK3CA E545K mutant cervical cancer; patient enrolled in Study D3610C00001 Part C), 11: adenocarcinoma, intestinal type; 12: melanoma.
Source: Figure 3B from Banerji et al 2018; cited as figure 9 in the CS 2.7.2 pg. 55

In the 5 patients treated with the "recommended phase 2 dose" (RP2D) and schedule (480 mg, 4 days on, 3 days off intermittent), there was an average decrease of 59% from baseline for pPRAS40, and 67% for pGSK3β. The magnitudes of these decreases were consistent with the PD responses required for preclinical efficacy and target inhibition with 480 mg BD 4 days on, 3 days off was stronger than with the 320 mg BD continuous dose.

Treatment with capivasertib also increased pAKT (consistent with ATP competitive mechanism of action), inhibited phosphorylation of 4EBP1, and resulted in an increase of FOXO nuclear translocation.

Robertson et al. 2020: STAKT

STAKT ("Short Term Effects of an AKT Inhibitor [AZD5363] on Biomarkers of the AKT Pathway and Anti-tumour Activity in a Breast Cancer Paired Biopsy") was a 2-stage, double-blind, randomised, placebo-controlled, 'window-of-opportunity' (pre-surgical paired biopsy) study in patients with newly diagnosed ER+ invasive breast cancer[5].

The primary objective was to compare the AKT pathway biomarker and anti-proliferative effect of 4.5 days' treatment with 3 dose levels of capivasertib monotherapy. Patients were randomised (1:1) in Stage 1 to either capivasertib 480 mg BD or placebo, and in Stage 2 to capivasertib 360 mg BD or 240 mg BD.

Tumour core biopsies were taken prior to the first dose and after 4.5 days of dosing (within 12 hours after the last dose), and levels of pPRAS40, pGSK3β, and Ki67 were measured using immunohistochemistry (IHC).

Treatment with capivasertib monotherapy at 480 mg BD for 4.5 days led to significant decreases from baseline in the H-score for the primary biomarkers, pPRAS40 and pGSK3β, compared to placebo.

As outlined in the methods part of the study, the H-score was calculated as the sum (% weak [1+]) + (% moderate [2+] x 2) + (% strong [3+] x 3), of staining localised in the cytoplasm and/or nucleus. Ki67 was evaluated by percentage nuclear positivity only.

A decrease of -39.0% ($p = 0.006$) for pGSK3β and -50.2% ($p < 0.0001$) for pPRAS40 ($n = 17$ samples for both) was observed.

Capivasertib treatment induced a reduction in cell proliferation as measured by Ki67 staining (-23.4%, $p = 0.052$).

Significant changes also occurred in secondary signalling biomarker pS6 (-30.0%, $p = 0.003$), while pAKT and nuclear FOXO3a increased in accordance with capivasertib's mechanism of action (pAKT: 117%, $p = 0.011$; FOXO3a nuclear: 844%, $p = 0.018$).

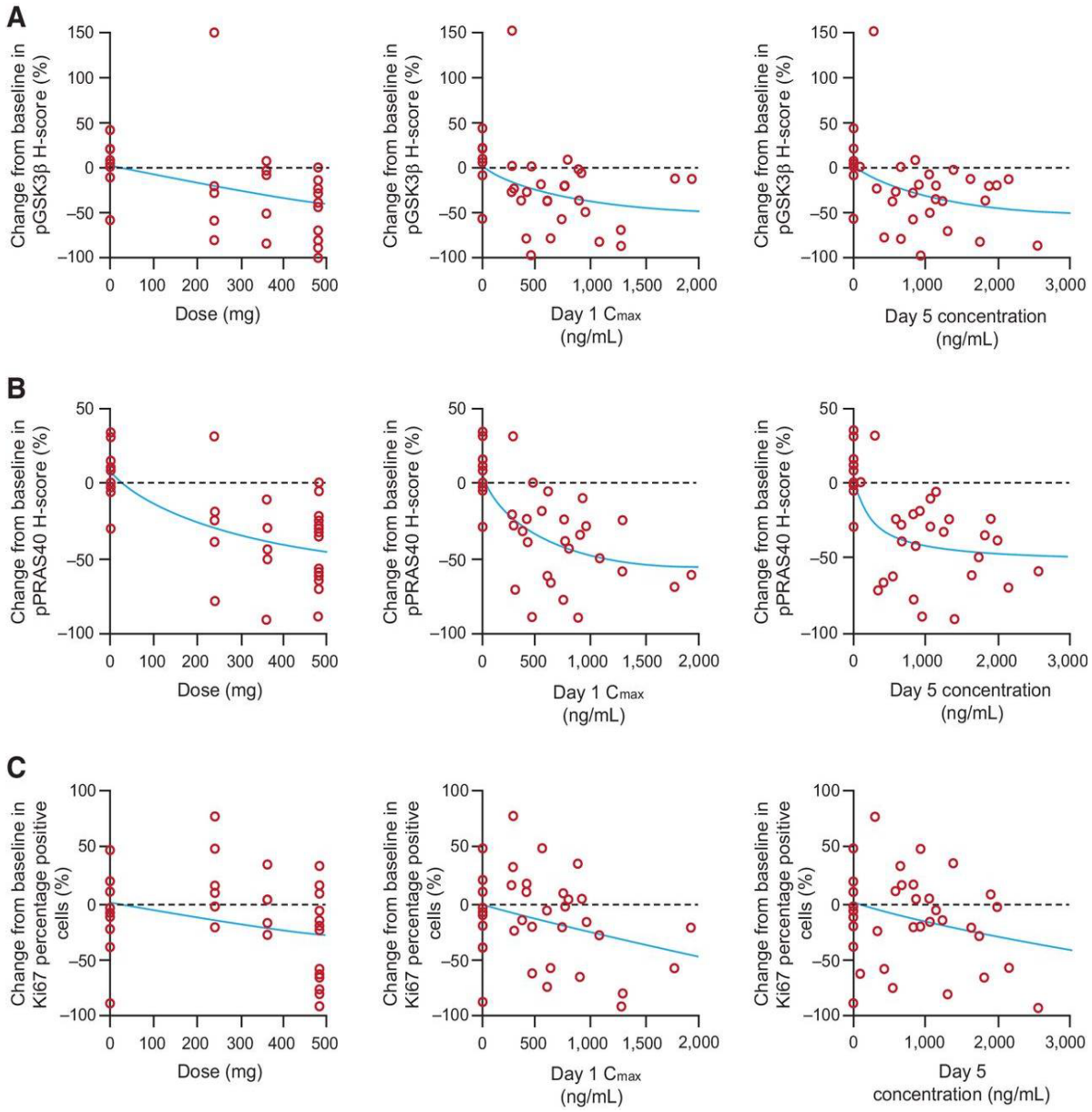
For the lower doses of capivasertib studied (360 mg BD and 240 mg BD), reductions in absolute and percentage pPRAS40 and pGSK3β were also observed, which were smaller in magnitude than the changes observed at 480 mg BD; although the number of samples analysed was small ($n = 5$ and $n = 6$, respectively).

According to Robertson et al. 2020, biomarker modulation was dose and concentration dependent. The dose–response relationship for percentage change from baseline could be described by a nonlinear (Emax) model for all primary biomarkers in the figure below.

Similar correlations were observed for the change in the biomarkers and PK exposure (Cmax on day 1 or concentration at the time of biopsy on day 5).

[5] John F.R. Robertson et al.; Proliferation and AKT Activity Biomarker Analyses after Capivasertib (AZD5363) Treatment of Patients with ERþ Invasive Breast Cancer (STAKT); Clin Cancer Res 2020;26:1574–85

Figure 7 STAKT: Observed and Model-predicted Dose- and Concentration- response Relationships for (A) pGSK3β, (B) pPRAS40, and (C) Ki67 as Percentage Change From Baseline



Secondary Pharmacology

Cardiac Electrophysiology

Based on an exposure-response analysis of centrally evaluated digital ECG data for patients with advanced solid malignancies who received capivasertib doses from 80 to 800 mg, the predicted mean QTcF prolongation was 3.87 ms (90% CI: 2.77, 4.97) at the mean steady state Cmax following 400 mg BD. See exposure/response analysis below.

Hyperglycaemia

Hyperglycaemia is an on-target adverse effect of inhibition of the PI3K/AKT/PTEN signalling pathway.

Rash

Rash was also discussed to be an adverse effect related to the inhibition of PI3K/AKT/PTEN signalling pathway.

Exposure-response analyses of efficacy following combination treatment with capivasertib + fulvestrant

To explore the relationship between capivasertib exposure parameters and the efficacy endpoints, PFS, ORR and OS, in patients with locally advanced or metastatic HR+/HER2-breast cancer following recurrence or progression on or after treatment with an AI who were treated with capivasertib + fulvestrant, exposure-response analyses of efficacy were performed using data for patients treated with capivasertib + fulvestrant in the pivotal CAPItello-291 study.

In the CAPItello-291 study, the PFS Kaplan-Meier curves for the Overall Population and the Altered Population showed no statistically significant differences between the quartiles of the exposure metrics (using the Benjamini-Hochberg method) at the dose level of 400 mg BD [4 days treatment/3 days off].

Cox proportional hazards models were developed and a stepwise covariate performed on the capivasertib arm in the Overall Population and the Altered Population. Capivasertib exposure was not a significant predictor of PFS at the dose level of 400 mg BD [4/3].

Exposure-response relationships between the exposure metrics and ORR did not show any statistically significant differences for the exposure metrics as quartiles or continuous, or for any covariate, in the Overall Population or in the Altered Population at the dose level of 400 mg BD [4/3].

It was concluded that there was no relationship between capivasertib PK exposure at the range observed from the dose and regimen that was studied in CAPItello-291 (400 mg BD [4/3]) and PFS or ORR in the Overall Population and the Altered Population.

Exposure-response analysis of safety following capivasertib monotherapy

Pooled pharmacokinetic and safety data from 277 patients who participated in three Phase I trials: First time in human (FTIH) (D3610C00001), Japanese safety/PK study (D3610C00004) and Formulation/food study (OAK, D3610C00007) were evaluated.

Patients received doses of 80 to 800 mg twice daily (BD), either with a continuous (daily) schedule, or with one of two intermittent schedules; 4 days on/3 days off ([4/3]) or 2 days on/5 days off ([2/5]).

The objectives of this analysis were to explore the relationship between exposure to capivasertib and incidence of AE leading to dose discontinuation, AE leading to dose modification (interruption and/or reduction), serious adverse event (SAE), AE grade ≥ 3, AE grade ≥ 1, diarrhoea AE grade ≥ 2, rash AE grade ≥ 2, hyperglycaemia AE grade ≥ 3 and increased blood glucose > 13.9 mmol/L in patients with solid tumours who were administered capivasertib as monotherapy.

Significant relationships were identified between the weekly dose (PWD) and/or weekly AUC (AUCPWD) and all safety endpoints evaluated, except for AEs of any grade which were observed in almost all patients.

Exposure-response analysis of safety following combination treatment with capivasertib + fulvestrant

Exposure-response analyses of safety were performed using data from 414 patients treated with capivasertib (400 mg BD 4 days on, 3 days off) + fulvestrant (500 mg IM on Days 1, 15 and 29 and once monthly thereafter) from the FTIH study (D3610C00001: 74 patients) and the CAPItello-291 study (340 patients).

The provided report concluded that based on the pooled data, the exposure-safety modelling predicted no clinically relevant relationship between capivasertib PK exposure and the investigated safety endpoints over the range of exposure observed in CAPItello-291 and these analyses do not indicate a need for a priori dose adjustments in any subgroup of patients.

Exposure-response analysis to evaluate QT/QTc interval prolongation for capivasertib

An exposure-response analysis of baseline-adjusted QTc interval was performed in patients with advanced or metastatic solid malignancies enrolled in the FTIH study (D3610C00001) (Parts A, B, C and D). Of 208 patients, 22 patients with no time-matched QT-PK measurements and 6 patients with no single dose data were excluded. As a result, in total, 503 measurements from 180 individuals, collected following single capivasertib administration of 80 to 800 mg, were used for the analysis.

Table 35 Predictions based on a prespecified concentration-QTcF model

Dose regimen	C_{max}[1] (ng/mL)	Mean ΔQTcF (ms)	Lower limit of ΔQTcF 90% CI (ms)	Upper limit of ΔQTcF 90% CI, (ms)
Continuous, 80 mg BD	172	0.34	-0.64	1.32
Continuous, 160 mg BD	653	1.95	1.04	2.87
Continuous, 240 mg BD	666	2.00	1.08	2.91
Continuous, 320 mg BD	982	3.06	2.07	4.05
Continuous, 400 mg BD	1223	3.87	2.77	4.97
Continuous, 480 mg BD	2030	6.58	4.92	8.24
Continuous, 600 mg BD	2936	9.62	7.20	12.04
4 days on/3 days off, 480 mg BD	1426	4.55	3.33	5.77
4 days on/3 days off, 640 mg BD	2721	8.90	6.66	11.13
2 days on/5 days off, 640 mg BD	2484	8.10	6.07	10.14
2 days on/5 days off, 800 mg BD	3856	12.71	9.46	15.95

1: Geometric mean of observed Cmax on day 8, Day 4, and Day 2 for continuous, 4 days on/3 days off and 2 days on/5 days off schedules, respectively.
Source: Exposure-Response Analysis Report; Population C-QT/QTc relationship analysis, table 8; pg. 26

As outlined above, observed Cmax at 400 mg BD continuous dosing on Day 8 was selected as an estimate of the therapeutic Css,max. Based on the model, mean QTcF increased with increasing Cmax. The predicted mean QTcF change from baseline is 3.87 ms (90% CI 2.77 ms -4.97 ms) at the estimated steady state at day 8 of Cmax 1223 ng/mL at the therapeutic dose (400 mg b.i.d. continuous dosing).

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Capivasertib (AZD5636) has been studied in healthy subjects and in participants with advanced solid malignancies with oral doses ranging from 80 mg to 600 mg twice daily [BD] (up to 800 mg BD for intermittent schedule).

The basic PK of capivasertib has been characterised using non-compartmental analysis in the Phase I ADME study (D3614C00007) in healthy subjects, and in Part A and Part B of the Phase I FTIH study (D3610C00001) of single and multiple doses of capivasertib in patients with advanced solid malignancies.

The potential effect of intrinsic and extrinsic factors on capivasertib PK has been quantitatively assessed in the Japanese safety/PK study (D3610C00004), formulation/food study (D3610C00007), food/PPI

study (D3614C00005), itraconazole DDI study (D3614C00004), midazolam DDI study (D3614C00003), RE-AKT (a study of capivasertib + enzalutamide in mCRPC), and using population PK analysis.

Population PK parameters for capivasertib have been estimated based on population PK analysis of data from a pool of Phase I, II, and III studies of capivasertib monotherapy, capivasertib + fulvestrant, and capivasertib + paclitaxel in patients with advanced solid malignancies, including the pivotal phase III CAPItello-291 study.

DDI predictions have been made using a PBPK model developed using both *in vitro* data and PK data from Phase I studies of capivasertib.

During the course of the development program, three different immediate release formulations were used: a drug in capsule formulation used in Phase 1 clinical studies, a Phase 2 film-coated tablet and an optimised film-coated tablet formulation used in Phase 3 studies. The commercial capivasertib film-coated tablets are qualitatively and quantitatively identical to the Phase 3 clinical film-coated tablets, but are differentiated through use of debossing. Bridging between the Phase 1 capsule and the Phase 2 film-coated tablet formulations was to be demonstrated via an *in viv*o relative bioavailability study (D3610C00007). Subsequent bridging between Phase 2 tablets and Phase 3 tablets was performed.

Study D3610C00007 was performed with multiple dosings, which is acceptable for an application with an oncology indication, but adds another source of variability in the study. Of note, the results are also outside of the 0.8-1.25 acceptance range, therefore not completely in line with the Guideline on the investigation of bioequivalence (BE). Conclusion on BE from this study was regarded tenuous at best and during the evaluation the applicant was requested to justify the bridging of the formulation. The applicant pointed out to similar PK (not BE but not expected significant differences in PD) between Phase I, Phase II and Phase III formulations. The quality assessment was acknowledged to go in the same direction. The CHMP in the end concluded that no additional bridging between formulations will be required.

Capivasertib has been assigned a BCS 4 classification (low solubility, low permeability) based on available solubility, permeability, and absolute bioavailability data which is considered acceptable.

Pharmacokinetic data from study D3614C00007 (ADME) in healthy volunteers (n=5 completers) showed that capivasertib is readily absorbed following a single oral dose of 400 mg capivasertib tablets with median tmax for Capivasertib was 1.74 h post-dose. The geometric mean apparent terminal plasma half-life for capivasertib was 12.9 h and the absolute bioavailability of Capivasertib following a 400 mg Capivasertib oral dose was 29%.

In subjects with advanced solid malignancies in study D3610C00001 (FTIH), following single oral doses of capivasertib, median tmax values ranged from 1.00 to 2.17 hours. The apparent terminal half-life was approximately 10 hours (range: 6.85 to 15.0 hours) and was independent of dose. Taking into consideration the small cohort sizes and the data variability, the geometric mean Cmax and AUC data from patients that had received 80 mg, 160 mg, 240 mg, 320 mg, 400 mg, 480 mg, 600 mg, 640 mg, or 800 mg AZD5363 appeared to be generally dose-proportional.

Following multiple bd oral doses, the plasma concentration-time profiles measured over the dosing interval, quantified from samples collected on Day 8 (continuous dosing), Day 4 (4 days on, 3 days off) and Day 2 (2 days on, 5 days off) of dosing, were generally consistent with the first 12 hours of the single dose profiles. The exposure (area under the plasma concentration-time curve from 0 hours to 12 hours) after multiple dosing was approximately 2 times the exposure reported after the first dose.

The systemic exposure (AUC and Cmax) increased proportionally over the dose range of 80 to 800 mg range after single dose administration in patients. After multiple-dose administration of 80 to 600 mg twice daily, the AUC increased slightly more than dose proportional. Following intermittent dosing of capivasertib 400 mg twice daily, 4 days on, 3 days off, the capivasertib steady-state AUC is

8 069 h ng/mL (37%) and Cmax is 1 371 ng/mL (30%). Concentrations are predicted to be attained on the 3rd and 4th dosing day of each week, starting from week 2. During the off-dosing days, the plasma concentrations are low (approximately 0.5% to 15% of the steady state Cmax).

Food effects were investigated in studies D3610C00007 and D3614C00005. The results of study D3610C00007 indicate that food reduced the rate and/or amount of AZD5363 absorption from the tablet formulation (Phase II tablet) and that the extent of exposure is only modestly decreased after fed and fasted administrations of the tablet. In the cross-over with the phase III formulation study D3614C00005, the comparison of high-fat, high-calorie breakfast to partially fasted conditions in line with the pivotal study showed an overall similar exposure (AUCinf 90% CI 0.99-1.29). This is also true for the comparison of low-fat, low-calorie breakfast to partially fasted conditions (AUC_{inf} 90% CI 0.88-1.05). The effect of a high-fat, high-calorie breakfast when compared to overnight fasting was modest (AUC_{inf} 90% CI 1.22-1.43). When capivasertib was administered after a high-fat, high-calorie meal (approximately 1000 kcal), the fed to fasted ratio was 1.32 and 1.23, for AUC and Cmax, respectively, compared to when given after an overnight fast. When capivasertib was administered after a low-fat, low-calorie meal (approximately 400 kcal), the exposure was similar to that after fasted administration with fed to fasted ratios of 1.14 and 1.21, for AUC and Cmax, respectively. Co-administration with food did not result in clinically relevant changes to the exposure.

Based on non-clinical data, capivasertib is not extensively bound to plasma proteins (percentage unbound 22.3%). The plasma to blood ratio was 0.714. The mean volume of distribution was 2.6 L/Kg after intravenous administration to healthy subjects.

The results of mass balance study D3614C00007 indicate that faecal excretion is the major route of elimination, while urinary excretion is the minor elimination pathway. An average of 95.1% of the radioactivity administered was recovered in excreta over the 168 h sampling period.

The effective half life after multiple dosing in patients was 8.3 h. The mean total plasma clearance was 38 L/h after a single IV administration to healthy subjects. The mean total oral plasma clearance was 60 L/h after single oral administration and decreased by 8% after repeated dosing of 400 mg twice daily. Following single oral dose of 400 mg, the mean total recovery of radioactive dose was 45% from urine and 50% from faeces. Renal clearance was 21% of total clearance. Capivasertib is primarily eliminated by metabolism.

The value of the effective half-life of 8.34 L is derived from population PK analysis based only on Phase 1 and Phase 2 data and not the final model including Phase 3 data. This is also the half-life reported in the SmPC (8.3 h). Since all studies have been conducted in patients and the model did not reveal a difference between study phases it is considered acceptable to base estimation of effective half-life only on the studies with rich sampling.

Results from *in vitro* studies suggest that capivasertib is primarily metabolised by CYP3A4 and UGT2B7 enzymes. Human metabolites of capivasertib were detected and quantified in Day 8 AUC pooled plasma samples from patients receiving 400 mg BD from the FTIH study D3610C00001.The major metabolite in human plasma was identified as an ether glucuronide (AZ14102143) that accounted for 83% of total drug-related material using nuclear magnetic resonance spectroscopy, and was inactive against AKT. A minor oxidative metabolite ("+3[O]") was detected and quantified at much lower levels (2%), while capivasertib accounted for 15% of total circulating drug-related material. No active metabolites have been identified. In urine, the major response was characterised as the ether glucuronide, and it was estimated that it represented 19% to 37% of the dose in urine.

As stated above, capivasertib is primarily metabolised by CYP3A4 and UGT2B7 enzymes. UGT2B7 was discussed to be an enzyme rich in single nucleotide polymorphisms (SNPs). There are currently no data

that indicate that genetic polymorphism of UGT2B7 would have a clinically relevant impact on the PK of capivasertib.

With regard to special populations, clinical pharmacology studies to specifically evaluate the role of impaired renal function, impaired hepatic function, age and gender have not been conducted.

Based on population pharmacokinetic analyses, AUC and Cmax were 1% higher in patients with mild renal impairment (creatinine clearance 60 to 89 mL/min), compared to patients with normal renal function. AUC and Cmax were 16% higher in patients with moderate renal impairment (creatinine clearance 30 to 59 mL/min), compared to patients with normal renal function. There is no data in severe renal impairment or end-stage renal disease (creatinine clearance < 30 ml/min). No dose adjustment is required for patients with mild or moderate renal impairment.

Based on population pharmacokinetic analyses, AUC and Cmax were 5% higher in patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN, or bilirubin > 1 ULN to ≤ 1.5 ULN), compared to patients with normal hepatic function (bilirubin ≤ ULN and AST ≤ ULN). AUC was 17% and Cmax was 13% higher in patients with moderate hepatic impairment (bilirubin > 1.5 ULN to ≤ 3 ULN), compared to patients with normal hepatic function. There is limited data in patients with moderate hepatic impairment and no data in severe hepatic impairment. No dose adjustment is required for patients with mild hepatic impairment.

Based on population pharmacokinetic analysis, AUC and Cmax showed that race (including White and Japanese patients), gender or age did not significantly impact the capivasertib exposure. There was a statistically significant correlation of apparent oral clearance of capivasertib to body weight. Compared to a patient with a body weight of 66 kg, a 47 kg patient is predicted to have 12% higher AUC. There is no basis for dose modification based on body weight as the predicted effect on capivasertib exposure was small.

Drug-drug interactions (DDI) have been discussed based on the provided results of *in vitro* studies using human biomaterial, the applicant´s own and published clinical studies (*in vivo*) in healthy volunteers and patients as well as PBPK modelling (*in silico*). The PBPK model cannot be accepted to predict drug interactions and potential dose adjustments. According to the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**) and draft ICH M12 guideline on drug interactions, when the candidate enzymes have been identified in vitro, the main metabolic pathways (≥25% of total elimination) generally require additional clinical characterisation to determine and quantify the risk of interaction with the investigational drug as a victim. Based on the shortcomings of the PBPK model, potential DDIs identified in *in vitro* investigation which have not yet been investigated *in vivo* have been identified to require additional clinical characterisation to determine and quantify the risk of interaction. During the evaluation, the applicant was asked to comment and outline how DDI risk as discovered in the in vitro studies can be further investigated in vivo and propose adequate amendments for the product information based on the currently available data. Section 4.5 of the SmPC has been revised accordingly and the applicant is strongly encouraged to further investigate potential DDIs with UGT1A1, CYP2D6 and CYP2B6 metabolizing enzymes (capivasertib as a perpetrator) (REC).

Co-administration of a single dose of capivasertib 400 mg after repeated dosing of acid-reducing agent rabeprazole 20 mg BID for 3 days in healthy subjects did not result in clinically relevant changes of the capivasertib exposure.

In vitro studies have demonstrated that capivasertib is primarily metabolised by CYP3A4 and UGT2B7 enzymes. In vivo, capivasertib is a weak, time-dependent inhibitor of CYP3A. Results of clinical drug-drug interaction (DDI) studies investigating potential DDI based on CYP3A4 interactions (itraconazole and enzalutamide) are cited below, clinical DDI studies investigating potential DDIs based on UGT2B7 interactions have not been performed.

Medicinal products that may increase capivasertib plasma concentrations

Strong CYP3A4 inhibitors

Coadministration of TRUQAP with strong CYP3A4 inhibitors increases capivasertib concentration, which may increase the risk of TRUQAP toxicity. Avoid coadministration with strong CYP3A4 inhibitors (e.g. boceprevir, ceritinib, clarithromycin, cobicistat, conivaptan, ensitrelvir, idelalisib, indinavir, itraconazole, josamycin, ketoconazole, lonafarnib, mibefradil, mifepristone, nefazodone, nelfinavir, posaconazole, ribociclib, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, tucatinib, voriconazole, grapefruit or grapefruit juice). If coadministration cannot be avoided, reduce the dose of TRUQAP. Co-administration of multiple 200 mg doses of the strong CYP3A4 inhibitor itraconazole increased capivasertib total exposure (AUCinf) and the peak concentration (Cmax) by 95% and 70%, respectively, relative to capivasertib given alone.

Moderate CYP3A4 inhibitors

Coadministration of TRUQAP with moderate CYP3A4 inhibitors increases capivasertib concentration, which may increase the risk of TRUQAP toxicity. Reduce the dose of TRUQAP when coadministered with moderate CYP3A4 inhibitor (e.g. aprepitant, ciprofloxacin, cyclosporine, diltiazem, erythromycin, fluconazole, fluvoxamine, tofisopam, verapamil).

Medicinal products that may decrease capivasertib plasma concentrations

Strong CYP3A4 inducers

Coadministration of TRUQAP with strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort) should be avoided. Coadministration of capivasertib with strong CYP3A4 inducer enzalutamide decreased the capivasertib AUC by approximately 40% to 50%.

Moderate CYP3A4 inducers

Coadministration of capivasertib with moderate CYP3A4 inducer has the potential to decrease the concentration of capivasertib. This may reduce the efficacy of TRUQAP. Coadministration of moderate CYP3A4 inducers should be avoided (e.g. bosentan, cenobamate, dabrafenib, elagolix, etravirine, lersivirine, lesinurad, lopinavir, lorlatinib, metamizole, mitapivat, modafinil, nafcillin, pexidartinib, phenobarbital, rifabutin, semagacestat, sotorasib, talviraline, telotristat ethyl, thioridazine).

Medicinal products whose plasma concentrations may be altered by capivasertib

Substrates of CYP3A

Concentration of medicinal products that are primarily eliminated via CYP3A metabolism may increase when coadministered with TRUQAP which may then lead to increased toxicity depending on their therapeutic window. Capivasertib increased the midazolam AUC by 15% to 77% and is therefore a weak CYP3A inhibitor (see section 5.2). Dose adjustment may be required for medicinal products that are primarily eliminated via CYP3A metabolism and have narrow therapeutic window (e.g. carbamazepine, cyclosporine, fentanyl, pimozide, simvastatin, tacrolimus).

CYP2D6 substrates with a narrow therapeutic index

In vitro evaluations indicated that capivasertib has a potential to inhibit the activities of CYP2D6 enzymes. Capivasertib should be used with caution in combination with sensitive substrates of CYP2D6 enzymes which exhibit a narrow therapeutic index because capivasertib may increase the systemic exposure of these substrates.

CYP2B6 substrates with a narrow therapeutic index

In vitro evaluations indicated that capivasertib has a potential to induce the activities of CYP2B6 enzymes. Capivasertib should be used with caution in combination with sensitive substrates of CYP2B6 enzymes which exhibit a narrow therapeutic index (e.g. bupropion) because capivasertib may decrease the systemic exposure of these substrates.

UGT1A1 substrates with a narrow therapeutic index

In vitro evaluations indicated that capivasertib has a potential to inhibit the activities of UGT1A1 enzymes. Capivasertib should be used with caution in combination with sensitive substrates of UGT1A1 enzymes which exhibit a narrow therapeutic index (e.g. irinotecan) because capivasertib may increase the systemic exposure of these substrates.

Interactions with hepatic transporters (BCRP, OATP1B1, OATP1B3)

The exposure of medicinal products that are sensitive to inhibition of BCRP, OATP1B1 and/or OATP1B3 if they are metabolised by CYP3A4, may increase by co-administration with TRUQAP. This may lead to increased toxicity. Depending on their therapeutic window, dose adjustment may be required for medicinal products that are sensitive to inhibition of BCRP, OATP1B1 and/or OATP1B3 if they are metabolised by CYP3A4 (e.g. simvastatin).

Interactions with renal transporters (MATE1, MATE2K, OCT2)

The exposure of medicinal products that are sensitive to inhibition of MATE1, MATE2K and/or OCT2 may increase by coadministration with TRUQAP. This may lead to increased toxicity. Depending on their therapeutic window, dose adjustment may be needed for medicinal products that are sensitive to inhibition of MATE1, MATE2K and OCT2 (e.g. dofetilide, procainamide). The SmPC of the other medicinal products should be consulted for the recommendations regarding coadministration with MATE1, MATE2K and/or OCT2 inhibitors. Transient serum creatinine increases may be observed during treatment with TRUQAP due to inhibition of OCT2, MATE1 and MATE2K by capivasertib.

Capivasertib inhibited CYP2C9, CYP2D6, CYP3A4 and UGT1A1 and induced CYP1A2, CYP2B6 and CYP3A4 metabolising enzymes in in vitro studies. It also inhibited BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1 and MATE2K drug transporters in vitro.

Clinical DDI studies investigating potential DDIs based on CYP1A2, CYP2B6, CYP2C9, CYP2D6, UGT1A1, BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1 and MATE2K interactions have not been performed.

Pharmacodynamics

Hyperglycaemia

Hyperglycaemia is an on-target adverse effect of inhibition of the PI3K/AKT/PTEN signalling pathway. Frequency and severity of adverse events related to hyperglycaemia and the possibility to manage these AEs with supportive treatments and/or capivasertib dose modification are discussed below in clinical efficacy and clinical safety sections.

Rash

Rash was also discussed to be an adverse effect related to the inhibition of PI3K/AKT/PTEN signalling pathway. Frequency and severity of adverse events related to "rash" and the possibility to manage these AEs with supportive treatments and/or capivasertib dose modification are discussed below in the clinical efficacy and clinical safety sections.

Exposure-response modelling of efficacy data has been performed on data from the pivotal CAPItello-291 study.

The relationship between capivasertib exposure and safety outcomes has been assessed using exposure-response modelling of data from a pool of Phase I studies of capivasertib monotherapy conducted in patients with advanced solid malignancies.

Exposure-response safety modelling has also been conducted on data from a pool of Phase I studies and the Phase III pivotal CAPItello-291 study in patients with advanced breast cancer who received capivasertib + fulvestrant. QT/QTc interval prolongation for capivasertib has been evaluated using exposure-response modelling of centrally evaluated digital ECG data from the FTIH study (D3610C00001).

During the evaluation it was concluded that the pharmacodynamic rationale for the treatment in the PIK3CA/AKT1/PTEN alteration negative population lacks further justification. It was finally concluded that due to the very limited efficacy in terms of PFS in the 'Known non-altered population' and the considerable toxicity for the combination treatment, the indication should be restricted to the PIK3CA/AKT1/PTEN altered population (see Clinical efficacy section).

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics, pharmacodynamic and interaction potential of capivasertib are considered sufficiently characterised and the relevant information has been included in sections 4.5 and 5.2 of the SmPC.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

The dosing regimen selection for the combination of capivasertib and fulvestrant was preceded by selection of the dosing regimen for capivasertib monotherapy.

In the FTIH study (D3610C00001) of capivasertib, a continuous and two intermittent dosing schedules were evaluated (all BD). The continuous schedule doses ranged from 80 mg to 600 mg, while the intermittent schedules tested 480 mg and 640 mg given 4 days on, 3 days off, or 640 mg and 800 mg, given 2 days on, 5 days off. The RP2Ds were 320 mg, 480 mg, and 640 mg for the 'continuous', '4 days on - 3 days off', and '2 days on - 5 days off' schedules, respectively. In each case, the number of DLTs observed at the next dose levels above in each schedule did not meet the threshold for a non-tolerated dose as defined in the clinical study protocol. However, based on the totality of the data, including chronic tolerability, the lower doses were selected as the RP2Ds.

Table 36 FTIH study (D3610C00001): Summary of dosing schedules studied and results

Study part	Dosing schedule	Dose and frequency [a]	Number of DLTs (number of evaluable patients)	Tolerability/ RP2D [b,c]
A (dose-escalation): capivasertib administered to patients with advanced solid malignancies	Schedule 1, **continuous**	**Capi 80 mg BD**	0 (5)	-
		Capi 160 mg BD	0 (5)	-
		Capi 240 mg BD	0 (6)	-
		Capi 320 mg BD	0 (12)	MWTD/RP2D
		Capi 400 mg BD	1 (11)	Not chronically tolerated
		Capi 480 mg BD	4 (6)	NTD

		Capi 600 mg BD	2 (2)	NTD
	Schedule 2, **intermittent** 4 days on, 3 days off	**Capi 480 mg BD**	0 (11)	MWTD/RP2D
		Capi 640 mg BD	0 (10)	Not chronically tolerated
	Schedule 2, **intermittent** 2 days on, 5 days off	**Capi 640 mg BD**	1 (8)	MWTD/RP2D
		Capi 800 mg BD	3 (14)	Not chronically tolerated
B (dose-expansion): capivasertib administered to patients with advanced solid malignancies	Schedule 1, **continuous**	**Capi 320 mg BD**	-	-
	Schedule 2, **intermittent** 4 days on, 3 days off	**Capi 480 mg BD**	-	-
C: capivasertib administered to patients with advanced or metastatic ER+ or HER2+ breast cancer or gynaecological (ovarian, cervical or endometrial) cancer, or other advanced solid cancer, that had a *PIK3CA* mutation	**Intermittent** 4 days on, 3 days off	**Capi 480 mg BD**	-	-
D: capivasertib administered to patients with advanced or metastatic ER+ or HER2+ breast cancer, gynaecological (ovarian, cervical or endometrial) cancer or other advanced solid cancer that had an *AKT1* mutation or other molecular aberration leading to dysregulation of the PI3K/AKT pathway	**Intermittent** 4 days on, 3 days off	**Capi 480 mg BD**	-	-
E: capivasertib in combination with background fulvestrant administered to patients with advanced or metastatic ER+ breast cancer that had an *AKT1* mutation	**Intermittent** 4 days on, 3 days off	**Capi 400 mg BD + fulvestrant 500 mg** on Days 1, 15 and 29, and once monthly thereafter	-	-
F: capivasertib in combination with background fulvestrant administered to patients with advanced or metastatic ER+ breast cancer that had a *PTEN* mutation	**Intermittent** 4 days on, 3 days off	**Capi 400 mg BD + fulvestrant 500 mg** on Days 1, 15 and 29, and once monthly thereafter	-	-

[a] Doses are presented in ascending order, which may differ from the order in which they were studied. Some doses/schedules were studied in parallel.

[b] According to the protocol: If 2 or more patients report a DLT in a group of up to 6 evaluable patients, the dose will be considered not tolerated.

[c] According to the protocol: Once the NTD is defined the MTD will be confirmed at the dose-level below the NTD or a dose between the NTD and the last tolerated dose will be investigated.

No further evaluation of capivasertib monotherapy was performed.

The recommended dose and dosing regimen of capivasertib in combination with fulvestrant was determined to be 400 mg BD, 4 days on, 3 days off for the Phase Ib part of FAKTION study (see section 3.8 Supportive study). Although no DLTs were observed at 400 mg, 480 mg was not explored in the interests of maintaining appropriate tolerability. The dose and schedule selected (400 mg BD, 4 days on,

3 days off) achieved exposure levels in a similar range to that required to achieve efficacy in ER+ breast cancer non-clinical models.

2.6.5.2. Main study(ies)

Study D3615C0000 (CAPItello-291): 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

EudraCT number: 2019-003629-78

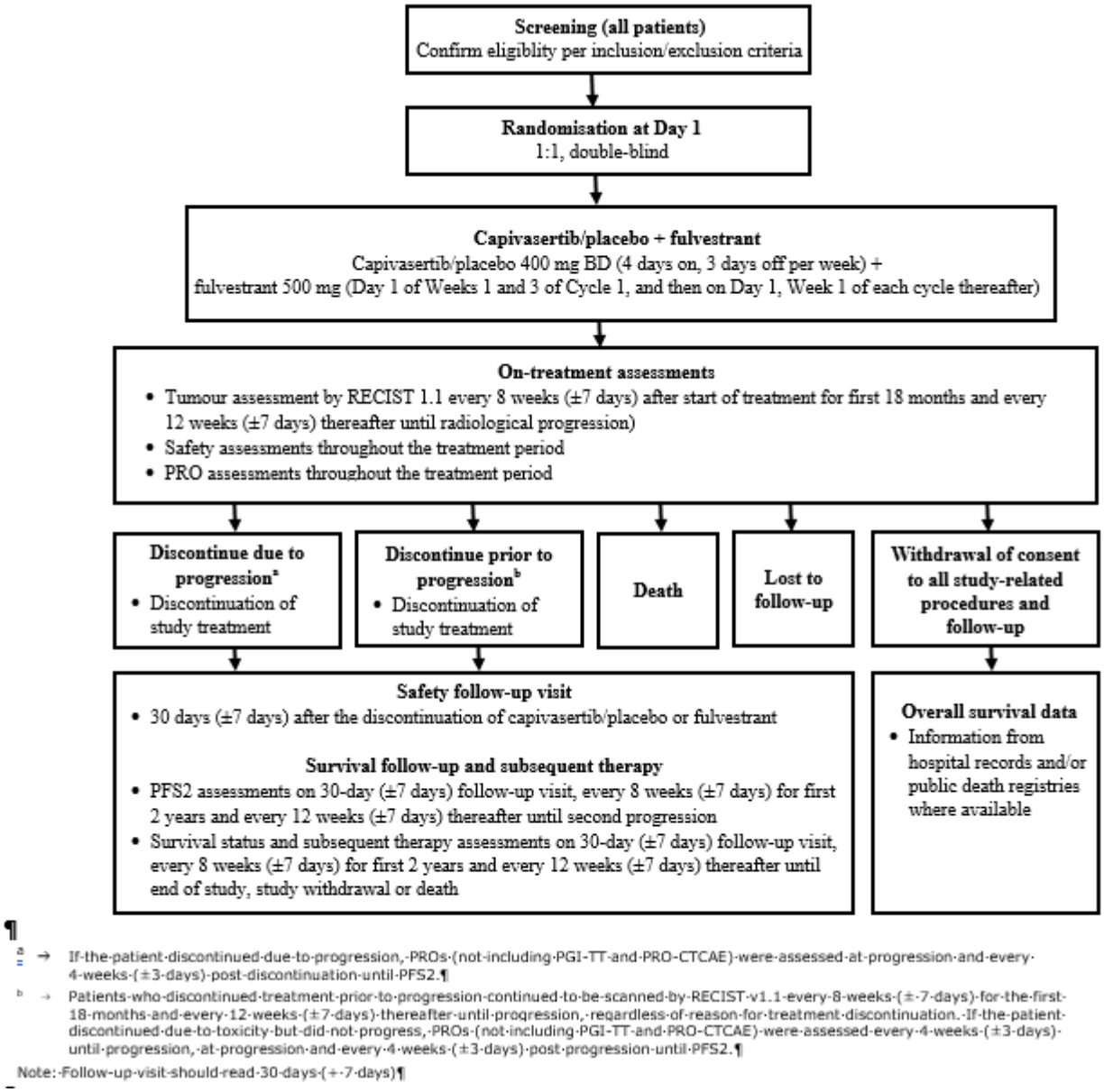
Methods

CAPItello-291 is the Phase III, double-blind, placebo-controlled, parallel-group, randomised, multicentre study to investigate the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant for the treatment of patients with HR+, HER2- locally advanced or metastatic breast cancer following disease recurrence or progression on or after aromatase inhibitor therapy, with or without a CDK4/6 inhibitor.

The study was powered to show a statistically significant difference between capivasertib + fulvestrant and placebo + fulvestrant in PFS in the *overall population* and the *altered population* (dual primary endpoints) and OS (key secondary endpoint) in the Overall Population; OS in the *altered population* was also assessed (see Protocol Version 4.0)

Clinical outcome was examined in the *overall population* of patients (i.e. regardless of tumour PIK3CA/AKT1/PTEN alteration status) as well as in a patient subgroup with tumours carrying at least one PIK3CA/AKT1/PTEN alteration (altered population).

Figure 8 Flow chart of study design



¶

[a] → If the patient discontinued due to progression, PROs (not including PGI-TT and PRO-CTCAE) were assessed at progression and every 4 weeks (±3 days) post discontinuation until PFS2.¶

[b] → Patients who discontinued treatment prior to progression continued to be scanned by RECIST v1.1 every 8 weeks (±7 days) for the first 18 months and every 12 weeks (±7 days) thereafter until progression, regardless of reason for treatment discontinuation. If the patient discontinued due to toxicity but did not progress, PROs (not including PGI-TT and PRO-CTCAE) were assessed every 4 weeks (±3 days) until progression, at progression and every 4 weeks (±3 days) post progression until PFS2.¶

Note: Follow-up visit should read 30 days (+ 7 days)¶

- **Study Participants**

Key inclusion criteria:

For inclusion in the study, patients had to fulfil the following criteria amongst others:

- **Informed consent**

1 For inclusion in the optional exploratory genetic and/or biomarker research, provision of signed and dated written genetic and/or biomarker informed consents, respectively, prior to collection of sample(s)

- **Age**

2 Patients aged ≥ 18 years (aged ≥ 20 years in Japan) at the time of signing the ICF

- **Type of patient and disease characteristics**

3 Adult females, pre- and/or post-menopausal, and adult males

- Pre-menopausal (and peri-menopausal, i.e., those that did not meet the criteria for post-menopausal defined below) women could be enrolled if amenable to treatment with an LHRH agonist. Patients were to have commenced concomitant treatment with LHRH agonist prior to or on Cycle 1, Day 1 and had to be willing to continue on it for the duration of the study.
- Post-menopausal women were defined as:
  - aged ≥ 60 years of age, or
  - aged < 60 years of age and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments/chemotherapy/ovarian suppression/tamoxifen or similar. These patients should also have had serum oestradiol and follicle stimulating hormone (FSH) levels confirmed as being within the standard laboratory reference range for post-menopausal females, OR
  - documented bilateral oophorectomy.

4 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 had to express ER with or without co-expression of progesterone receptor. Therefore, tumours had to be:

- ER+ defined as ≥ 1% of tumour cells stain positive for ER on immunohistochemistry (IHC) or, if no percentage was available, then an Allred IHC score of ≥ 3/8,
- PR+ defined as ≥ 1% of tumour cells stain positive for progesterone receptor on IHC or, if no percentage was available, then an Allred IHC score of ≥ 3/8; or PR- defined as < 1% of tumour cells stain positive for progesterone receptor on IHC or, if no percentage was 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 ISH, or if IHC not done, no evidence of amplification on ISH.

5 Metastatic or locally advanced disease with radiological or objective evidence of recurrence or progression (the cancer should have shown progression during or after most recent therapy); locally advanced disease must not have been amenable to resection with curative intent (patients who were considered suitable for surgical or ablative techniques following potential down-staging with study treatment were not eligible).

6 Patients were 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 did not need to be the most recent therapy)

7 Patients had to have:

- at least 1 lesion, not previously irradiated, that could be measured accurately at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which had to have short axis ≥ 15 mm) with CT or MRI which was 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 could be assessed by CT or MRI; patients with sclerotic/osteoblastic bone lesions only in the absence of measurable disease were not eligible.

8 Patients had to be eligible for fulvestrant therapy as per local investigator assessment.

9 Consented to submit and provide a mandatory FFPE tumour sample for central testing.

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

- **Reproduction**

11 Pre-menopausal patients with ovarian suppression induced by LHRH agonist should have agreed to use 2 forms of highly effective methods of accepted contraception to prevent pregnancy during the study and for 2 years after the last dose of fulvestrant, or until 16 weeks after discontinuing capivasertib/placebo whichever occurred later.

12 Male patients should have used barrier contraception (i.e., condoms) from the time of screening until 2 years after the last dose of fulvestrant or until 16 weeks after discontinuation of capivasertib/placebo, whichever occurred later.

Main exclusion criteria:

- **Medical conditions**

1 A disease burden that made the patient ineligible for endocrine therapy per the investigator's best judgement (e.g., symptomatic visceral disease that was potentially life-threatening in the short-term).

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).

3 Radiotherapy with a wide field of radiation within 4 weeks prior to study treatment initiation (capivasertib/placebo) and/or radiotherapy with a limited field of radiation for palliation within 2 weeks prior to study treatment initiation (capivasertib/placebo).

4 Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.

5 Any of the following cardiac criteria:

- Mean resting QT interval corrected by Fridericia's formula (QTcF) > 470 msec obtained from 3 consecutive ECGs
- Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block)
- Any factors that increased the risk of corrected QT interval (QTc) prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, potential for torsades de pointes, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age or any concomitant medication known to prolong the QT interval
- Experience of any of the following procedures or conditions in the preceding 6 months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure NYHA grade ≥ 2

- Uncontrolled hypotension – systolic blood pressure < 90 mmHg and/or diastolic blood pressure < 50 mmHg
- Cardiac ejection fraction outside institutional range of normal or < 50% (whichever was higher) as measured by ECHO (or MUGA scan if an ECHO could not be performed or was inconclusive).

6 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).

7 Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:

- Absolute neutrophil count < 1.5×10^9/L
- Platelet count < 100×10^9/L
- Haemoglobin < 9 g/dL (< 5.59 mmol/L). [**NOTE:** any blood transfusion had to be > 14 days prior to the determination of a haemoglobin ≥ 9 g/dL (≥ 5.59 mmol/L)]
- Alanine aminotransferase (ALT) and AST > 2.5 times ULN if no demonstrable liver metastases or > 5 × ULN in the presence of liver metastases
- Total bilirubin > 1.5 × ULN (Patients with confirmed Gilbert's syndrome could be included in the study)
- Creatinine > 1.5 × ULN concurrent with creatinine clearance < 50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance was only required when creatinine was > 1.5 × ULN.

8 As judged by the investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV), including those who had confirmed COVID-19. Screening for chronic conditions was not required. Known abnormalities in coagulation such as bleeding diathesis, or treatment with anticoagulants precluding intramuscular injections of fulvestrant or LHRH agonist (if applicable).

9 Previous allogenic bone marrow or solid organ transplant.

10 Known immunodeficiency syndrome.

11 History of hypersensitivity to active or inactive excipients of capivasertib, fulvestrant and LHRH agonists (if applicable, i.e., concomitant LHRH agonist required in this study) or drugs with a similar chemical structure or class to capivasertib, fulvestrant or LHRH agonists (if applicable, i.e., concomitant LHRH agonist required in this study).

- **Prior/concomitant therapy**

12 More than 2 lines of endocrine therapy for inoperable locally advanced or metastatic disease.

13 More than 1 line of chemotherapy for inoperable locally advanced or metastatic disease. Adjuvant and neoadjuvant chemotherapy were not classed as lines of chemotherapy for ABC.

14 Prior treatment with any of the following:

- AKT, PI3K and mTOR inhibitors

- Fulvestrant, and other SERDs
- 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.
- Any concomitant medication that may have interfered with fulvestrant safety and efficacy based on the prescribing information of fulvestrant and local clinical guidelines.

- **Other exclusions**

15 Pregnant women (confirmed with positive pregnancy test) or breast-feeding women.

- **Treatments**

Patients received capivasertib 400 mg BD (2 tablets of 200 mg taken BD; total daily dose 800 mg) given on an intermittent weekly dosing schedule 4 days on, 3 days off or placebo. Where possible, doses were to be taken in a fasted state from at least 2 hours prior to the dose to at least 1-hour post-dose 12 hours apart at approximately the same time each day, and fulvestrant (at the approved dose regimen of 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).

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

Pre- or peri-menopausal patients were to have commenced concomitant treatment with LHRH agonist prior to or on Cycle 1, Day 1 and had to be willing to continue LHRH agonist treatment for the duration of the study. Male patients could receive concomitant LHRH agonist if deemed appropriate by the investigator.

LHRH analogues were not considered as IMP.

For capivasertib dose reductions (level 1: 320 mg BD and level 2 200 mg BD) were permitted, re-escalation was not allowed. For general capivasertib-related toxicities any intolerable AE or AE grade G ≥3 led to dose reduction, for specific AE – hyperglycaemia, maculo-papular rash and other skin reactions, and diarrhoea- the protocol provided specific advice.

Dose interruptions were recommended for substantial acute toxicities as medically indicated.

A maximum break of 28 consecutive days for capivasertib/placebo dosing was allowed within each treatment cycle or between two consecutive cycles. A maximum delay of 35 days since a planned injection of fulvestrant was allowed.

Patients were required to return all bottles of study medication, and the number of tablets remaining was counted by the research nurse/pharmacist/investigator. Data regarding capivasertib/placebo dosing were collected.

- **Objectives**

The primary objective was to show superiority on the effect of capivasertib + fulvestrant vs placebo + fulvestrant by assessment of PFS in the *overall population* and in the PIK3CA/AKT1/PTEN-altered subgroup.

- **Outcomes/endpoints**

Table 37 Objectives and endpoints

Objectives [a]	Endpoints
Primary	
• To compare the effect of capivasertib + fulvestrant relative to placebo + fulvestrant by assessment of PFS in the *overall population* and in the *PIK3CA/AKT1/PTEN*-altered subgroup (see Protocol Version 4.0, Section 3).	• PFS is defined as the time from randomisation until progression per RECIST v1.1, as assessed by the investigator at the local site, or death due to any cause.
Secondary	
• To compare the effect of capivasertib + fulvestrant relative to placebo + fulvestrant by assessment of OS in the *overall population* and in the *PIK3CA/AKT1/PTEN*-altered subgroup (see Protocol Version 4.0, Section 3).	• OS is length of time from randomisation until the date of death due to any cause.
• To compare the effect of capivasertib + fulvestrant relative to placebo + fulvestrant by assessment of PFS2 in the *overall population* and in the *PIK3CA/AKT1/PTEN*-altered subgroup (see Protocol Version 4.0, Section 3).	• PFS2 is defined as the time from randomisation until second progression on next-line treatment, as assessed by the investigator at the local site, or death due to any cause.
• To compare the effect of capivasertib + fulvestrant relative to placebo + fulvestrant by assessment of ORR in the *overall population* and in the *PIK3CA/AKT1/PTEN*-altered subgroup (see Protocol Version 4.0, Section 3).	• ORR is defined as the percentage of patients with at least one CR or PR per RECIST v1.1, as assessed by the investigator at the local site.
• To compare the effect of capivasertib + fulvestrant relative to placebo + fulvestrant by assessment of DoR in the *overall population* and in the *PIK3CA/AKT1/PTEN*-altered subgroup (see Protocol Version 4.0, Section 3).	• 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 (see Protocol Version 4.0, Section 3).	• CBR is defined as the percentage of patients who have a CR, PR or stable disease per RECIST v1.1 (without subsequent cancer therapy) maintained ≥ 24 weeks after randomisation.
• To assess the safety and tolerability of capivasertib + fulvestrant as compared to placebo + fulvestrant in the *overall population* and in the *PIK3CA/AKT1/PTEN*-altered subgroup.	• Safety and tolerability will be evaluated in terms of AEs/SAEs, vital signs, clinical chemistry/haematology/ glucose metabolism parameters, and ECG parameters. For full details of the assessments, refer to Protocol Version 4.0, Table 3).
• To evaluate the PK of capivasertib when given in combination with fulvestrant.	• Plasma concentration of capivasertib pre-dose (C_{trough}) and post-dose (C_{1h} and C_{4h}) in the *overall population* (patients randomised to capivasertib + fulvestrant). • AUC_{0-12h}, C_{max} and t_{max} in a subpopulation of approximately 6 Japanese patients with rich PK sampling.

• To assess the impact of capivasertib + fulvestrant vs placebo + fulvestrant on patients' disease-related symptoms, function and HRQoL in the *overall population* and in the *PIK3CA/AKT1/PTEN*-altered subgroup where applicable (see Protocol Version 4.0, Section 3).	• Evaluation of EORTC QLQ-C30, EORTC QLQ-BR23, scale/item scores including change from baseline and time to deterioration.
• To compare the effect of capivasertib + fulvestrant relative to placebo + fulvestrant by assessment of time to definitive deterioration of ECOG performance status from baseline in the *overall population* and in the *PIK3CA/AKT1/PTEN*-altered subgroup (see Protocol Version 4.0, Section 3).	• Time to definitive deterioration of ECOG performance status is defined as time from randomisation to the earlier of the date of the first definitive deterioration or death due to any cause.

[a] The *PIK3CA/AKT1/PTEN*-altered subgroup is referred to as the 'Altered Population' in this CSR.
Exploratory objectives are not included in the CSR Synopsis, but can be found in the CSR.

Imaging for PFS was performed using CT or MRI scans of the chest, abdomen and pelvis (with additional anatomy as clinically indicated by extent of disease) at baseline and 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.

Bone scans were performed at baseline and further if clinically indicated.

If the patient progressed or died immediately after two or more consecutive missed visits, the patient was to be censored at the time of the latest evaluable RECIST v1.1 assessment prior to the two missed visits.

- **Sample size**

The study was powered to show a statistically significant difference in OS between capivasertib + fulvestrant and placebo + fulvestrant in the Overall Population. It was also sufficiently powered to assess PFS in the PIK3CA/AKT1/PTEN-altered population (Altered Population) and overpowered to assess PFS in the Overall Population.

Assuming a significance level of 5%, a total of 492 OS events will be required to achieve 90% power to detect a treatment effect of an average hazard ratio of 0.74 in the Overall Population, assuming a 12-month delay to a treatment effect and a hazard ratio of 0.64 after the delay. Assuming 70% maturity at the time of the final analysis, approximately 700 patients were planned to be randomised to receive either capivasertib + fulvestrant or placebo + fulvestrant. Of these 700 randomised patients, it was expected that a minimum of 280 patients would have a tumour harbouring an eligible PIK3CA/AKT1/PTEN alteration, based on a prevalence of approximately 40% to 45%.

The PFS primary analysis took place after PFS reached 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% to 45% (and 174 events will have been observed if a test failure rate is 20%). Assuming a significance level of 3.5%, a total of 542 PFS events would provide > 99% power to detect a treatment effect of hazard ratio 0.64 in the overall population. Given the estimated sample size of the Altered Population and assuming a significance level of 5% following recycling of the remaining 3.5% alpha, a total of 217 PFS events (approximately 77% maturity) would provide 90.8% power to detect a treatment effect of hazard ratio 0.64 in the Altered Population. A median PFS of 5.5 months was assumed for the placebo + fulvestrant arm. At DCO1 (15 August 2022) the actual maturity was 77.8% (551 events) in the overall population, and 81.7% (236 events) in the altered population.

- **Randomisation and blinding (masking)**

Eligible patients were randomised in a 1:1 ratio to each arm of the global cohort in a blinded manner. Randomisation was stratified on the following factors:

- Liver metastases (yes vs no)
- Prior use of CDK4/6 inhibitors (yes vs no)
- Geographic location:
  - Region 1: United States, Canada, Western Europe, Australia, and Israel
  - Region 2: Latin America, Eastern Europe and Russia
  - Region 3: Asia.

Randomisation continued in China after randomisation of the global cohort was complete, and data from the China cohort was to be reported separately. Chinese patients randomised prior to the last patient first visit of the global cohort were also included in the global cohort (n = 8).

Capivasertib and placebo film-coated tablets were identical in appearance and presented in the same packaging to ensure blinding of the capivasertib.

- **Statistical methods**

Analysis sets

Full Analysis Set (FAS) (Overall Population): This comprised all patients randomised into the study, excluding patients randomised in China after the global cohort last patient first visit (LPFV). The FAS was analysed according to randomised treatment regardless of the treatment received (ITT principle). The FAS was used as the primary population for reporting efficacy data (including PROs) and to summarise baseline characteristics.

Altered Subgroup FAS (Altered Population): This comprised all patients included in the FAS with a PIK3CA/AKT1/PTEN altered tumour determined by central testing.

Safety Analysis Set (SAS): The SAS comprised all patients included in the FAS, who received at least one dose of study drug (fulvestrant, capivasertib, placebo) and were analysed according to the treatment received.

Progression-free survival 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 anti-cancer therapy prior to progression (i.e. date of PFS event or censoring – date of randomisation + 1). Progression-free survival was assessed by investigator assessment. A sensitivity analysis of PFS by BICR is also reported.

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

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

The dual primary endpoint PFS in the Overall Population based on the investigator RECIST v1.1 was analysed using a log-rank test stratified by randomisation stratification factors. To estimate the effect of treatment, the HR together with its 95% CI and CI adjusted for multiplicity were estimated from a stratified Cox proportional hazards model. Kaplan-Meier plots of PFS were 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 were provided along with the median PFS for each treatment group.

The dual primary endpoint of PFS in the Altered Population was analysed in the same way. In an exploratory analysis, progression-free survival in the Non-altered Population, including the Known Non-altered Population and the No Result Population, was analysed as described for the PFS in the Overall Population.

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 anti-cancer therapy (i.e. date of death or censoring – date of randomisation + 1). Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive.

The secondary endpoint OS was analysed using similar methodology as described for the primary PFS endpoint (hypothesis testing was not planned at data cut-off 1).

PFS2 was analysed using the same methodology as described for the primary PFS endpoint.

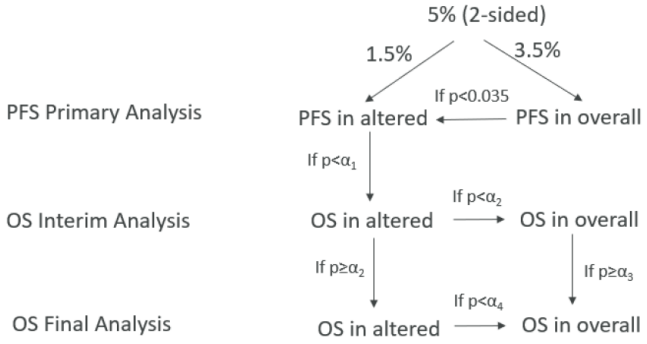
Objective response rate was analysed for both the Overall Population and the Altered Population. The ORR was compared between capivasertib + fulvestrant vs placebo + fulvestrant using logistic regression models adjusting for the stratification factors.

Descriptive data were provided for the duration of response (DoR) and clinical benefit rate (CBR).

Adjustment for multiplicity

To control the family-wise error rate in the strong sense at 5% for the treatment comparisons in OS and PFS, a predefined multiple testing procedure (MTP) with an alpha-exhaustive recycling strategy (Burman et al. 2009) taking into account intrinsic correlation between test statistics (Spiessens and Debois 2010), was applied. The MTP is outlined in the figure below. 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.

Figure 9 Illustration of DCOs and associated treatment comparisons



Following FDA's advice, a small alpha spend was applied to the assessment of no OS detriment at the time of the PFS primary analysis. This used a bespoke alpha spending function with 0.0001 alpha assigned to DCO1 in each of the Overall Population and the Altered Population. The remaining OS analyses will use the planned cumulative alpha at DCO2 and DCO3 from the 2-look O'Brien & Fleming method. 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). The OS Final Analysis will take place when approximately 70% maturity has been observed in both the Overall Population and the Altered Population.

Results

- **Participant flow**

A total of 901 patients were enrolled in 181 centres in 19 countries worldwide, of which193 patients were screen failures. A total of 708 patients were randomised to receive treatment with capivasertib + fulvestrant (n = 355) or placebo + fulvestrant (n = 353).

Three patients in the placebo + fulvestrant arm did not receive treatment: one died before its first dose, one withdrew consent, and the reason for the other was unknown.

At the time of DCO1, a higher proportion of patients continued to receive treatment in the capivasertib + fulvestrant arm compared with the placebo + fulvestrant arm (20.0% vs 12.3%). The most common reasons for discontinuing capivasertib/placebo (≥ 5% of patients) were breast cancer progression (58.9%) and adverse event (AE) (12.4%) in the capivasertib + fulvestrant arm, and breast cancer progression (78.0%) in the placebo + fulvestrant arm.

Figure 10 Patient disposition (all patients)

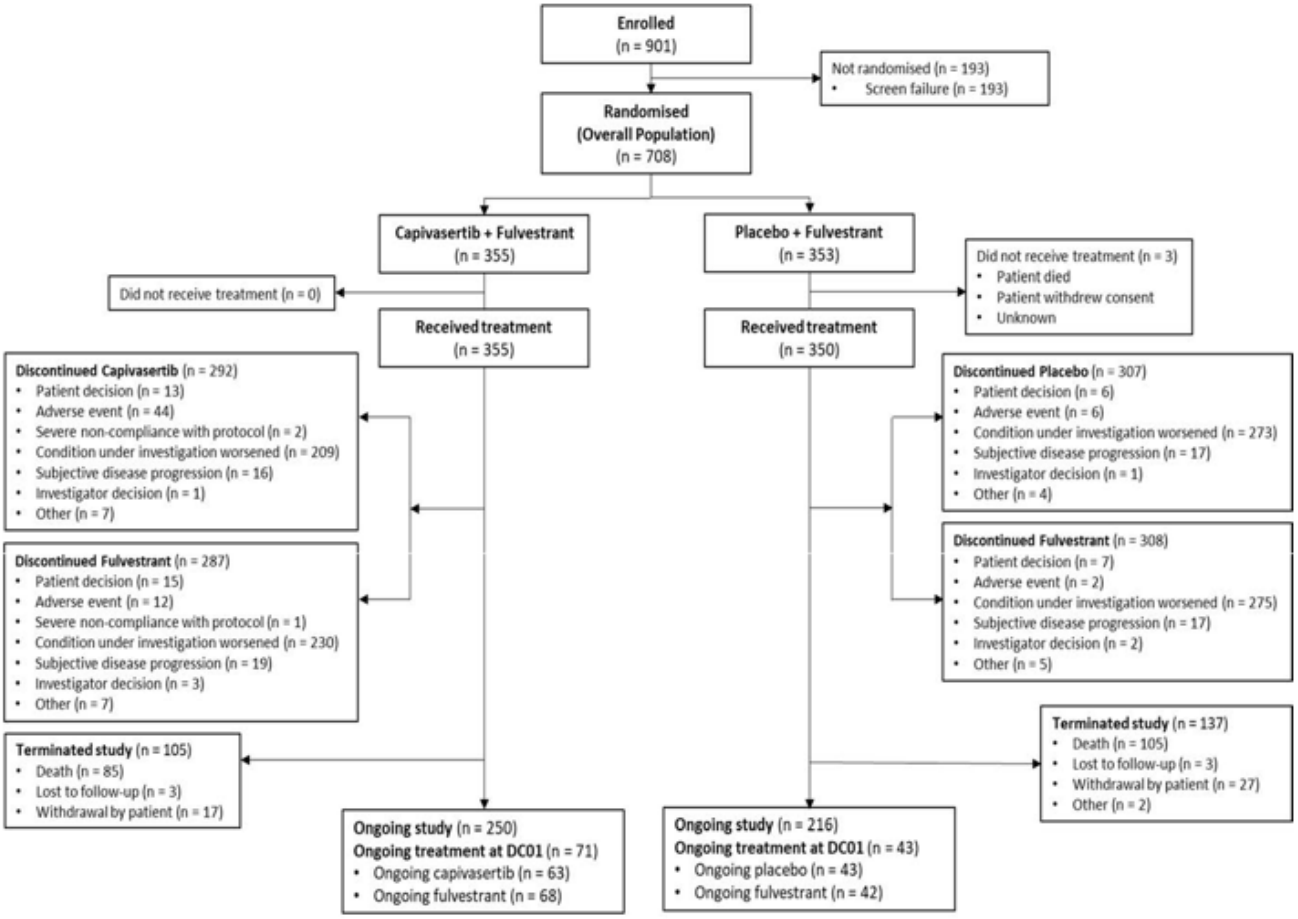
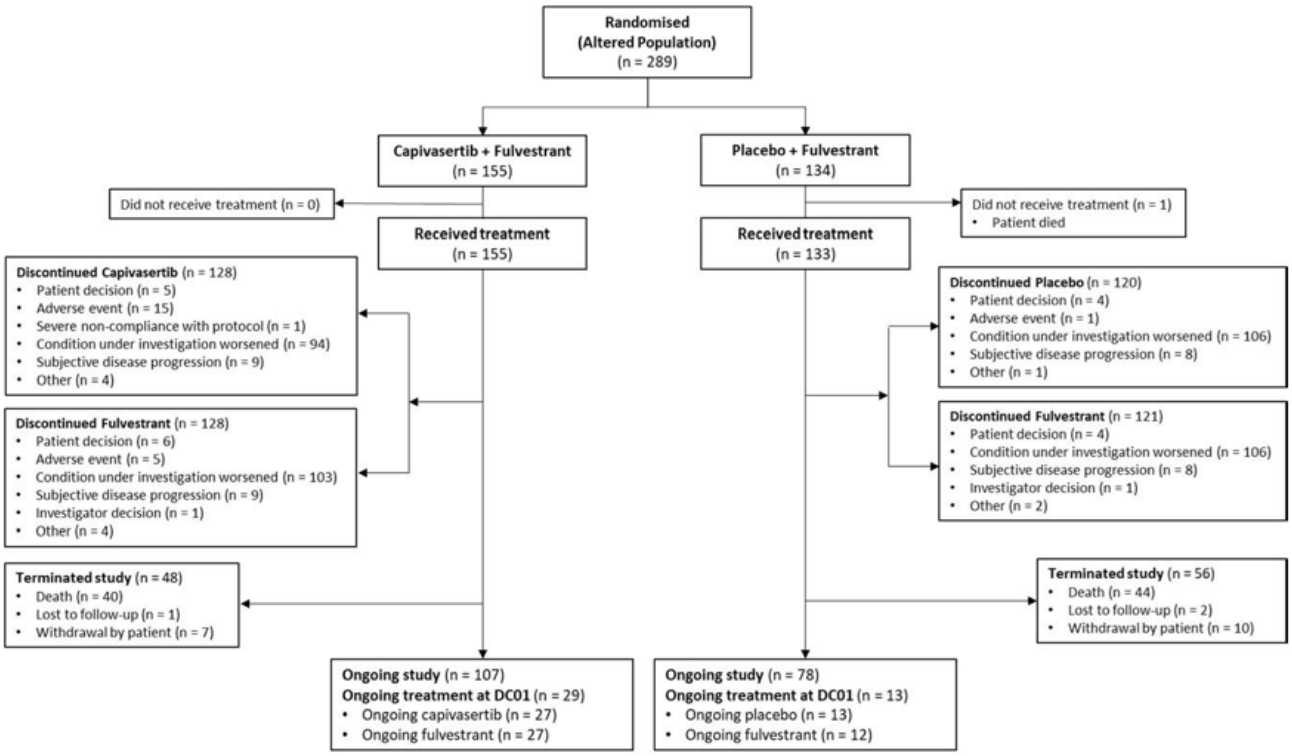


Figure 11 Patient disposition (altered population)



Source: Table 14.1.1.2 and Listing 16.2.1.1.

- **Recruitment**

The first patient was randomised on 02 June 2020 and the last patient was randomised into the Global cohort on 13 October 2021.

Patients were enrolled as follows:

- Region 1 (112 centres in United States, Canada, Western Europe, Australia, and Israel: 395 patients)
- Region 2 (23 centres in Latin America, Eastern Europe and Russia: 136 patients)
- Region 3 (46 centres in Asia, 177 patients).

The first DCO date for the study that is the basis for the submitted study report is 15 August 2022 (DCO1). At DCO1, the median duration of follow-up (defined as time to censoring or death) in all patients in the capivasertib + fulvestrant and placebo + fulvestrant arms was 14.9 and 14.3 months, respectively.

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

- **Conduct of the study**

The original study protocol (Version 1.0, dated 04 November 2019) was amended 3 times.

Table 38 Main protocol amendments

Amendment Number/Date	Main key details of amendment	Main reason(s) for amendment
Amendments made *before* the start of participant recruitment		
None		
Amendments made *after* the start of participant recruitment		
	Key secondary endpoints were updated.	To elevate ORR and CBR in the *overall population* to key secondary endpoints.
	Changes to wording of inclusion criterion 5, inclusion of females	To clarify details of menopausal status.
	Changes to wording of inclusion criterion 6, confirmation of breast cancer	To clarify definition of HER2-
	Changes to wording of inclusion criterion 7, metastatic or locally advanced disease with radiological or objective evidence of recurrence or progression	To clarify that the cancer should have shown progression during or after most recent therapy

Amendment Number/Date	Key details of amendment	Main reason(s) for amendment
	Clarified wording regarding the China cohort, and removed inclusion of patients from Taiwan in the China cohort. Removed the restriction on the biomarker test result for China patients to join global cohort FAS.	For clarification.
	Clarified FAS to comprise patients randomised into the study prior to global cohort LPFV; clarified the SAS would also include patients who received only fulvestrant and these patients would be included in the treatment arm to which they were randomised; clarified the Altered Subgroup FAS would include patients with a result from a valid biomarker test as pre- specified in the SAP.	For clarification.
	Added text to state that the remaining alpha will be recycled to test the study secondary endpoints if the OS endpoint is successful, and to specify the hierarchical testing order.	To specify the hierarchical testing order to test secondary endpoints after OS
CSP Version 3.0/ 29 June 2021	Clarified the FAS is to comprise patients randomised into the study, excluding patients randomised in China after the global cohort LPFV	For clarification of the cut-off for the definition of global cohort FAS.
	~~Removed reference to Asian population analyses~~	~~For simplification.~~

Amendment Number/Date	Key details of amendment	Main reason(s) for amendment
CSP Version 4.0/ 08 February 2022	Clarification of primary objectives. The primary objective was renamed as dual primary: PFS in the *overall population* and PFS in the *PIK3CA/AKT1/PTEN*-altered subgroup	The study was designed with an alpha split between the *overall population* and the *PIK3CA/AKT1/PTEN*-altered subgroup; however, only the *overall population* was defined as the primary endpoint. To render the nomenclature consistent with the intent of the multiple testing procedure, the primary objective was renamed as dual primary.
	Removed the interim PFS analysis for the Overall Population	To align with the change to the dual primary endpoints of PFS in the *overall population* and *PIK3CA/AKT1/PTEN*-altered subgroup.
	Duplication of all secondary objectives (except PK), so they are assessed in both the *overall population* and the *PIK3CA/AKT1/PTEN*-altered subgroup	To align with the dual primary endpoints.
	Clarification of the data cut-off trigger for primary PFS analysis as well as OS interim and final analysis	To align with the dual primary endpoints, the triggers of these DCOs were to be based on reaching the prespecified maturity both in the *overall population* and the *PIK3CA/AKT1/PTEN*-altered subgroup
	ORR added to exploratory objective and definition added to endpoint	To support the PFS analysis in various biomarker subgroups
	Updates to the MTP. With the removal of the PFS interim analysis, the 0.1% alpha originally reserved for the interim PFS analysis was allocated to test PFS in the Overall Population. The MTP was updated to allow alpha recycling from PFS in the *overall population* to the *PIK3CA/AKT1/PTEN*-altered subgroup. The testing sequence of the key secondary endpoints was amended.	To maximise the chance of success in PFS in the *PIK3CA/AKT1/PTEN*-altered subgroup.
	Definition of altered subgroup China FAS and China altered subgroup safety analysis set added, along with an updated timing for the China efficacy analysis	To align with the updated planned analysis for the global cohort.

[a] The changes in CSP Version 2.0 (03 June 2021) came into effect with CSP Version 3.0 (29 June 2021).

Important protocol violation were reported for 8.8% of patients, the majority concerned use of prior medication, for details see below.

Table 39 Important protocol deviations (overall population)

Important protocol deviation [a]	Number (%) of patients		
	Capivasertib + Fulvestrant (N = 355)	Placebo + Fulvestrant (N = 353)	Total (N = 708)
Number of patients with at least 1 important deviation	38 (10.7)	24 (6.8)	62 (8.8)
Patients who deviate from key entry criteria per the Clinical Study Protocol [b]	17 (4.8)	9 (2.5)	26 (3.7)
Inclusion Criterion 6 (histologically confirmed HR+/HER2− breast cancer)	1 (0.3)	0	1 (0.1)
Inclusion Criterion 9 (criterion for measurable lesion)	1 (0.3)	0	1 (0.1)
Inclusion Criterion 11 (consent to FFPE tumor sample for central testing)	1 (0.3)	0	1 (0.1)
Exclusion Criterion 21 (more than 1 line of chemotherapy for inoperable locally advanced or metastatic disease)	1 (0.3)	0	1 (0.1)
Exclusion Criterion 22 (prior medication use)	12 (3.4)	9 (2.5)	21 (3.0)
Missing	1 (0.3)	0	1 (0.1)
Randomised patients received capivasertib/placebo at incorrect dose for more than 4 days during any treatment cycle	13 (3.7)	3 (0.8)	16 (2.3)
Fulvestrant administered 4 or more days prior planned per protocol/label date (D28 or D14 depending on cycle)	9 (2.5)	3 (0.8)	12 (1.7)
Non-compliance with screening procedure protocol requirements (RECIST v1.1 tumor assessment not performed or not performed within screening period of 28 days)	0	4 (1.1)	4 (0.6)
Patient randomised but did not receive study treatment	0	3 (0.8)	3 (0.4)
Failure to complete or comply with inclusion/exclusion criteria (IC#2; IC#6; IC#7; IC#8; IC#9; IC#11; IC#13; EC#2; EC#5; EC#10; EC#14; EC#20; EC#21; EC#22) for cases not covered by program protocol deviations	0	1 (0.3)	1 (0.1)
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 John's Wort])	0	1 (0.3)	1 (0.1)

[a] Important deviations before the start of treatment and during treatment, as per SAP, are reported in this table.

[b] Patients allocated to treatment who were subsequently discovered to fail the eligibility criteria.

Specific inclusion/exclusion criteria defined as IPD are listed in the PDMP.

The same patient may have had more than 1 important protocol deviation.

Impact of COVID-19 pandemic

All patients were randomised into the study after the start of the COVID-19 pandemic. The proportion of patients in the FAS with 1 or more disruptions due to the pandemic was low (37 patients, 5.2%), and was similar between treatment arms. The majority of disruptions were impacts on study visits (32 patients, 4.5%). Six patients (0.8%) had study drug impacted, and 1 patient (0.1%) withdrew from the study due to COVID-19.

Biomarker test and assignment to populations

PIK3CA/AKT1/PTEN alterations were identified by FoundationOne®CDx (F1CDx) and classified as altered or non-altered, as per the biomarker rules described in CSR Appendix 16.1.13. According to the CSR the samples were analysed retrospectively.

- **Baseline data**

The overall study population had a median age of 58.0 years including 30.7% patients > 65 years. Most patients were women (99.0%), most patients were White (57.5%) followed by Asian (26.7%). Median weight was 65.5 kg with a very wide range (34-150 kg), in line with the inclusion criteria 99.7% of patients presented with ECOG 0-1. The majority of patients was in postmenopausal state (77.3%).

Metastatic disease state was predominant (98.2%), most commonly located in bone and locomotor sites (73.0%), liver (43.9%) and lung (27.4%). At initial diagnosis the most common histology was invasive ductal carcinoma, 33.1 % presented with American Joint Committee on Cancer (AJCC) stage IV.

All tumours were tested ER positive, the majority developed secondary endocrine resistance.

All patients enrolled in the study were treated with previous endocrine therapy and, i.e. an AI, 44.6 % had also received tamoxifen. 76.1% had been treated with 1 line of endocrine treatment in the locally advanced/metastatic setting. The majority had received CDK 4/6 inhibitors (70.1 %).

49.4% had been treated with chemotherapy in the (neo)adjuvant setting and 18.2 % had received chemotherapy in the locally advanced/metastatic setting.

Details on patient characteristics, disease characteristics and prior treatment are given in the following tables.

Table 40 Patient and disease characteristics

	Overall Population			Altered Population		
	Capivasertib + fulvestrant (N = 355)	**Placebo + fulvestrant (N = 353)**	**Total (N = 708)**	**Capivasertib + fulvestrant (N = 155)**	**Placebo + fulvestrant (N = 134)**	**Total (N = 289)**
Median age, years (range)	59.0 (26, 84)	58.0 (26, 90)	58.0 (26, 90)	58.0 (36, 84)	60.0 (34, 90)	59.0 (34, 90)
Age group, n (%)						
< 50 years	76 (21.4)	99 (28.0)	175 (24.7)	27 (17.4)	29 (21.6)	56 (19.4)
≥ 50 to < 65 years	164 (46.2)	152 (43.1)	316 (44.6)	83 (53.5)	60 (44.8)	143 (49.5)
≥ 65 to < 75 years	91 (25.6)	76 (21.5)	167 (23.6)	37 (23.9)	28 (20.9)	65 (22.5)
≥ 75 years	24 (6.8)	26 (7.4)	50 (7.1)	8 (5.2)	17 (12.7)	25 (8.7)
Sex, n (%)						
Male	3 (0.8)	4 (1.1)	7 (1.0)	2 (1.3)	0	2 (0.7)
Female	352 (99.2)	349 (98.9)	701 (99.0)	153 (98.7)	134 (100)	287 (99.3)
Race, n (%)						
Black or African American	4 (1.1)	4 (1.1)	8 (1.1)	2 (1.3)	1 (0.7)	3 (1.0)
White	201 (56.6)	206 (58.4)	407 (57.5)	75 (48.4)	76 (56.7)	151 (52.2)
Other [a]	52 (14.6)	47 (13.3)	99 (14.0)	29 (18.7)	21 (15.7)	50 (17.3)
WHO / ECOG PS, n (%)						
(0) Normal activity	224 (63.1)	241 (68.3)	465 (65.7)	93 (60.0)	97 (72.4)	190 (65.7)
(1) Restricted activity	131 (36.9)	111 (31.4)	242 (34.2)	62 (40.0)	36 (26.9)	98 (33.9)
(2) In bed less than or equal to 50% of the time	0	1 (0.3)	1 (0.1)	0	1 (0.7)	1 (0.3)
Weight (kg)						
Mean (SD)	67.7 (16.19)	68.8 (16.90)	68.3 (16.55)	67.9 (14.63)	69.1 (16.81)	68.4 (15.66)
Median	65.0	66.5	65.7	65.8	66.7	66.0
Range	34-150	37-147	34-150	44-115	37-124	37-124
Diabetic status						
Diabetes	34 (9.6)	20 (5.7)	54 (7.6)	18 (11.6)	8 (6.0)	26 (9.0)
No Diabetes	321 (90.4)	333 (94.3)	654 (92.4)	137 (88.4)	126 (94.0)	263 (91.0)

Table 41 Illness characteristics

	Overall Population			Altered Population		
	Capivasertib + fulvestrant (N = 355)	**Placebo + fulvestrant (N = 353)**	**Total (N = 708)**	**Capivasertib + fulvestrant (N = 155)**	**Placebo + fulvestrant (N = 134)**	**Total (N = 289)**
Overall disease classification, n (%)						
Locally advanced [c]	6 (1.7)	6 (1.7)	12 (1.7)	0	2 (1.5)	2 (0.7)
Missing [d]	0	1 (0.3)	1 (0.1)	0	0	0
Metastatic [b]	349 (98.3)	346 (98.0)	695 (98.2)	155 (100)	132 (98.5)	287 (99.3)
Bone and locomotor	261 (73.5)	256 (72.5)	517 (73.0)	123 (79.4)	99 (73.9)	222 (76.8)
Liver	156 (43.9)	155 (43.9)	311 (43.9)	72 (46.5)	52 (38.8)	124 (42.9)
Lung	109 (30.7)	85 (24.1)	194 (27.4)	53 (34.2)	37 (27.6)	90 (31.1)
Distant lymph nodes	57 (16.1)	65 (18.4)	122 (17.2)	24 (15.5)	30 (22.4)	54 (18.7)
AJCC Stage IV	116 (32.7)	118 (33.4)	234 (33.1)	50 (32.3)	44 (32.8)	94 (32.5)
Menopausal status (females only), n (%)						
Pre/peri-menopausal	65 (18.3)	89 (25.2)	154 (21.8)	23 (14.8)	29 (21.6)	52 (18.0)
Post-menopausal	287 (80.8)	260 (73.7)	547 (77.3)	130 (83.9)	105 (78.4)	235 (81.3)
Receptor status						
ER+/PR+	255 (71.8)	246 (69.7)	501 (70.8)	116 (74.8)	101 (75.4)	217 (75.1)
ER+/PR-	94 (26.5)	103 (29.2)	197 (27.8)	35 (22.6)	31 (23.1)	66 (22.8)
ER+/PR unknown	5 (1.4)	4 (1.1)	9 (1.3)	4 (2.6)	2 (1.5)	6 (2.1)
ER- d	1 (0.3)	0	1 (0.1)	0	0	0
Type of endocrine resistance, n (%)						
Primary	127 (35.8)	135 (38.2)	262 (37.0)	60 (38.7)	55 (41.0)	115 (39.8)
Secondary	228 (64.2)	218 (61.8)	446 (63.0)	95 (61.3)	79 (59.0)	174 (60.2)

[d] One patient did not have any site of disease as during the treatment phase it was discovered that the lung lesion with which patient was randomised was not metastasis but primary lung cancer.

Table 42 Prior treatments

	Overall Population			Altered Population		
	Capivasertib + fulvestrant (N = 355)	**Placebo + fulvestrant (N = 353)**	**Total (N = 708)**	**Capivasertib + fulvestrant (N = 155)**	**Placebo + fulvestrant (N = 134)**	**Total (N = 289)**
Prior hormonal therapy, n (%)						
Aromatase inhibitor	355 (100)	353 (100)	708 (100)	155 (100)	134 (100)	289 (100)
Tamoxifen	157 (44.2)	155 (43.9)	312 (44.1)	69 (44.5)	57 (42.5)	126 (43.6)

	Overall Population			Altered Population		
	Capivasertib + fulvestrant (N = 355)	**Placebo + fulvestrant (N = 353)**	**Total (N = 708)**	**Capivasertib + fulvestrant (N = 155)**	**Placebo + fulvestrant (N = 134)**	**Total (N = 289)**
Prior CDK4/6 inhibitors, n (%)						
Yes	247 (69.6)	249 (70.5)	496 (70.1)	113 (72.9)	93 (69.4)	206 (71.3)
No	108 (30.4)	104 (29.5)	212 (29.9)	42 (27.1)	41 (30.6)	83 (28.7)
Treatment not approved	23 (21.3)	25 (24.0)	48 (22.6)	10 (23.8)	11 (26.8)	21 (25.3)
Treatment not affordable or not reimbursed	26 (24.1)	19 (18.3)	45 (21.2)	10 (23.8)	5 (12.2)	15 (18.1)
Tolerability concerns						
Haematologic	1 (0.9)	1 (1.0)	2 (0.9)	1 (2.4)	1 (2.4)	2 (2.4)
Non-haematologic	1 (0.9)	0	1 (0.5)			
Patient's preference	15 (13.9)	18 (17.3)	33 (15.6)	7 (16.7)	7 (17.1)	14 (16.9)
Healthcare provider's preference	39 (36.1)	40 (38.5)	79 (37.3)	13 (31.0)	17 (41.5)	30 (36.1)
Prior chemotherapy, n (%)						
(Neo)adjuvant treatment only	145 (40.8)	148 (41.9)	293 (41.4)	62 (40.0)	61 (45.5)	123 (42.6)
Locally advanced (inoperable) / metastatic treatment	65 (18.3)	64 (18.1)	129 (18.2)	30 (19.4)	23 (17.2)	53 (18.3)
Prior (neo)adjuvant chemotherapy, n (%)						
Yes	180 (50.7)	170 (48.2)	350 (49.4)	79 (51.0)	67 (50.0)	146 (50.5)
No	175 (49.3)	183 (51.8)	358 (50.6)	76 (49.0)	67 (50.0)	143 (49.5)
Prior lines of endocrine-based therapy for locally advanced (inoperable) or metastatic disease [e]						
0	39 (11.0)	54 (15.3)	93 (13.1)	13 (8.4)	20 (14.9)	33 (11.4)
1	287 (80.8)	252 (71.4)	539 (76.1)	131 (84.5)	96 (71.6)	227 (78.5)
2	29 (8.2)	47 (13.3)	76 (10.7)	11 (7.1)	18 (13.4)	29 (10.0)
Prior lines of endocrine-based therapy for locally advanced (inoperable) or metastatic disease – aromatase inhibitor containing regimens						
0	42 (11.8)	56 (15.9)	98 (13.8)	15 (9.7)	21 (15.7)	36 (12.5)
1	301 (84.8)	275 (77.9)	576 (81.4)	136 (87.7)	103 (76.9)	239 (82.7)
2	12 (3.4)	22 (6.2)	34 (4.8)	4 (2.6)	10 (7.5)	14 (4.8)
Prior lines of therapy for locally advanced (inoperable) or metastatic disease (includes endocrine or chemotherapy)						
0	37 (10.4)	52 (14.7)	89 (12.6)	12 (7.7)	20 (14.9)	32 (11.1)
1	235 (66.2)	208 (58.9)	443 (62.6)	107 (69.0)	79 (59.0)	186 (64.4)
2	73 (20.6)	77 (21.8)	150 (21.2)	31 (20.0)	29 (21.6)	60 (20.8)
3	10 (2.8)	16 (4.5)	26 (3.7)	5 (3.2)	6 (4.5)	11 (3.8)

[e] Race data for France, Hungary, Belgium were not allowed to be collected per local regulations and were recorded as 'other.'
[f] Metastatic disease - patient has any metastatic site of disease.
[g] Locally advanced - patient has only locally advanced sites of disease.
[h] One patient did not have any site of disease as during the treatment phase it was discovered that the lung lesion with which patient was randomised was not metastasis but primary lung cancer.
[i] Endocrine maintenance therapy was counted as a separate line.
The number of patients with data was used as the denominator for calculating percentages.

Details on type of the PIK3CA/AKT1/PTEN alteration status are that 44.2 % of the ITT belong to the confirmed non-altered subgroup, 40.8 % to the confirmed altered subgroup and 15.0 % to the unknown, i.e. no-result subgroup. More patients with confirmed PIK3CA/AKT1/PTEN alteration were randomised to the capivasertib+fulvestrant treatment group (43.7% vs 38.0%). Approximately 70% of PIK3CA/AKT1/PTEN alterations were alterations of PIK3CA only.

Table 43 Summary of PIK3CA/AKT1/PTEN alteration status (overall population)

***PIK3CA/AKT1/PTEN* alteration status**	**Number (%) of patients**		
	Capivasertib + Fulvestrant (N = 355)	**Placebo + Fulvestrant (N = 353)**	**Total (N = 708)**
Altered	**155 (43.7)**	**134 (38.0)**	**289 (40.8)**
PIK3CA only [a, b]	110 (31.0)	92 (26.1)	202 (28.5)
AKT1 only [a, b]	18 (5.1)	15 (4.2)	33 (4.7)
PTEN only [a, b]	21 (5.9)	16 (4.5)	37 (5.2)
PIK3CA and *AKT1* [a]	2 (0.6)	2 (0.6)	4 (0.6)
PIK3CA and *PTEN* [a]	4 (1.1)	9 (2.5)	13 (1.8)
Non-altered	200 (56.3)	219 (62.0)	419 (59.2)
Known non-altered (confirmed non-altered) [c]	**142 (40.0)**	**171 (48.4)**	**313 (44.2)**
No result (unknown)	**58 (16.3)**	**48 (13.6)**	**106 (15.0)**
FFPE not provided	10 (2.8)	4 (1.1)	14 (2.0)
Not done (preanalytical failure)	39 (11.0)	34 (9.6)	73 (10.3)
Not evaluable (post analytical failure)	9 (2.5)	10 (2.8)	19 (2.7)

[a] Mutually exclusive groups.
[b] Patients with co-occurring mutations are excluded from single gene count.
[c] All patients included in the *overall population* with no qualifying alterations in PIK3CA, AKT1 and PTEN in their tumour, as determined by central testing. Patients with unknown PIK3CA/AKT1/PTEN alteration status were excluded from this subgroup.
Source: Table 14.1.14.

The following 2 below tables provide details on the type of previous treatment classes prior to study and post-study. Post-study 49.4 % of patients received further treatment, the majority being chemotherapy (43.2%), much less patients received further hormonal treatment (11.7 %) or targeted treatment (9.0 %).

Table 44 Previous disease-related treatment classes (overall population)

Previous treatment classes	**Number (%) of patients**		
	Capivasertib + Fulvestrant (N = 355)	**Placebo + Fulvestrant (N = 353)**	**Total (N = 708)**
Immunotherapy	3 (0.8)	1 (0.3)	4 (0.6)

Hormonal therapy	355 (100)	353 (100)	708 (100)
Aromatase inhibitor	355 (100)	353 (100)	708 (100)
Tamoxifen	157 (44.2)	155 (43.9)	312 (44.1)
Cytotoxic chemotherapy	210 (59.2)	212 (60.1)	422 (59.6)
Targeted therapy	247 (69.6)	249 (70.5)	496 (70.1)
CDK4/6 inhibitor	247 (69.6)	249 (70.5)	496 (70.1)
Antiangiogenic therapy	11 (3.1)	9 (2.5)	20 (2.8)
Radiopharmaceuticals	0	0	0
PARP inhibitor	5 (1.4)	0	5 (0.7)
Biologic therapy	5 (1.4)	8 (2.3)	13 (1.8)
Experimental therapy	0	2 (0.6)	2 (0.3)
Other	25 (7.0)	33 (9.3)	58 (8.2)

Other category includes other not experimental anti-cancer therapies, past LHRH analogue, prior denosumab or bisphosphonate if it was considered as anti-cancer by investigator.

Patients may appear under more than one previous therapy class, if they have received more than one treatment.

Table 45 Post-discontinuation disease-related anti-cancer therapy (overall population)

	Number (%) of patients		
Anti-cancer therapy [a]	**Capivasertib + Fulvestrant (N = 355)**	**Placebo + Fulvestrant (N = 353)**	**Total (N = 708)**
Total number of patients	238 (67.0)	264 (74.8)	502 (70.9)
Immunotherapy	9 (2.5)	3 (0.8)	12 (1.7)
Hormonal therapy	98 (27.6)	107 (30.3)	205 (29.0)
Cytotoxic chemotherapy	199 (56.1)	216 (61.2)	415 (58.6)
Targeted therapy	67 (18.9)	91 (25.8)	158 (22.3)
Antiangiogenic therapy	22 (6.2)	29 (8.2)	51 (7.2)
PARP inhibitor	3 (0.8)	8 (2.3)	11 (1.6)
Biologic therapy	4 (1.1)	4 (1.1)	8 (1.1)
Experimental therapy	2 (0.6)	1 (0.3)	3 (0.4)
Other	4 (1.1)	3 (0.8)	7 (1.0)

[a] Therapies post-discontinuation of study treatment.

Patients may have more than one cancer therapy.

Source: Table 14.1.19.1.

The applicant also provided baseline patient and disease characteristics by either menopausal status, by prior treatment with CDK 4/6 inhibitors and PIK3CA/AKT1/PTEN alteration status, i.e. confirmed non-altered, unknown.

Prior CDK 4/6 inhibitor use was specifically addressed. Reasons not to use were predominantly health care providers preference, CDK 4/6 inhibitors not affordable or reimbursed, and CDK 4/6 inhibitors not approved.

In comparison to the CDK 4/6 inhibitors treated subgroup, the CDK 4/6 inhibitors naïve subgroup had a higher median age, less patients with pre/peri menopausal status, less AJCC stage IV at diagnosis, more (neo)adjuvant chemotherapy and substantially more patients with no prior endocrine based therapy for locally advanced or metastatic breast cancer (40.6% vs 1.4%). The proportion of CDK 4/6 inhibitors

naïve patients was higher in region 3 and 2 than in 1 (46.2% vs 31.6 % vs 22.2% of the CDK 4/6 inhibitors naïve population originated from the respective region). Thus, 47/395 patients (11.9%) in region 1 (including Western Europe, North America) and 98/177 patients (55.4%) in region 3 (Asia) were naïve to CDK 4/6 inhibitors.

In comparison to the postmenopausal subgroup, the pre/peri menopausal subgroup included more patients with AJCC stage IV at diagnosis and liver metastases, more patients treated with CDK 4/6 inhibitors and less patients with PIK3CA/AKT1/PTEN alterations.

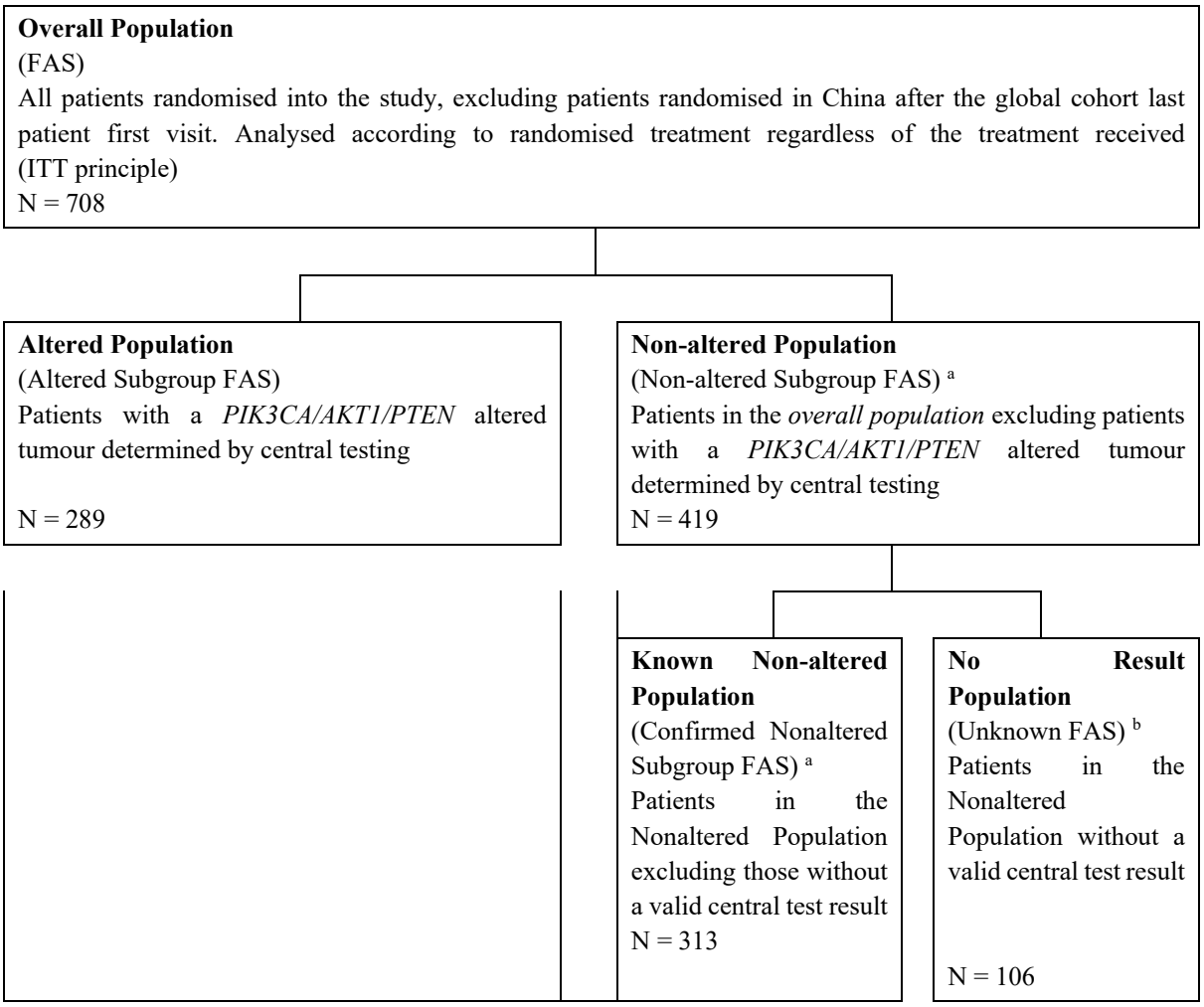
- **Numbers analysed**

The primary analysis populations for reporting efficacy data and to summarise baseline characteristics were as follows:

- The *overall population* (FAS) was analysed according to randomised treatment regardless of the treatment received (ITT principle).
- The *altered population* (Altered Subgroup FAS).

In addition, exploratory analyses for the complementary *non-altered population* are provided and the *non-altered population* is further divided in the *Known Non-altered Population*, and the *No Result Population*.

Figure 12 Efficacy population terminology



[a] Pre-specified exploratory population.

[b] Post hoc exploratory population.

Three DCOs (PFS primary [DCO1], OS interim and OS final) are planned for the pivotal CAPItello-291 study. Results for DCO1 (15 August 2022) are submitted in this marketing authorisation application.

Table 46 CAPItello-291 Planned DCOs

DCO	Analysis	(Estimated) Date [b]	Number of Events (Maturity of Data) [a]	
			Overall Population	*altered population* [c]
DCO1	PFS primary	15 August 2022	542 (77%)	217 (77%)
DCO2	OS interim (assuming 80% information fraction)	March 2024	394 (56%)	158 (56%)
DCO3	OS final	May 2025	492 (70%)	197 (70%)

For each specified analysis, the planned analysis DCO is expected to occur when the required number of events have been observed in the overall population and similar maturity has been reached in the Altered Population.

Estimated date for DCO2 and DCO3.

[a] Assuming N = 280 for the Altered Population.

- **Outcomes and estimation**

Primary endpoint: Progression-free survival PFS (investigator assessment)

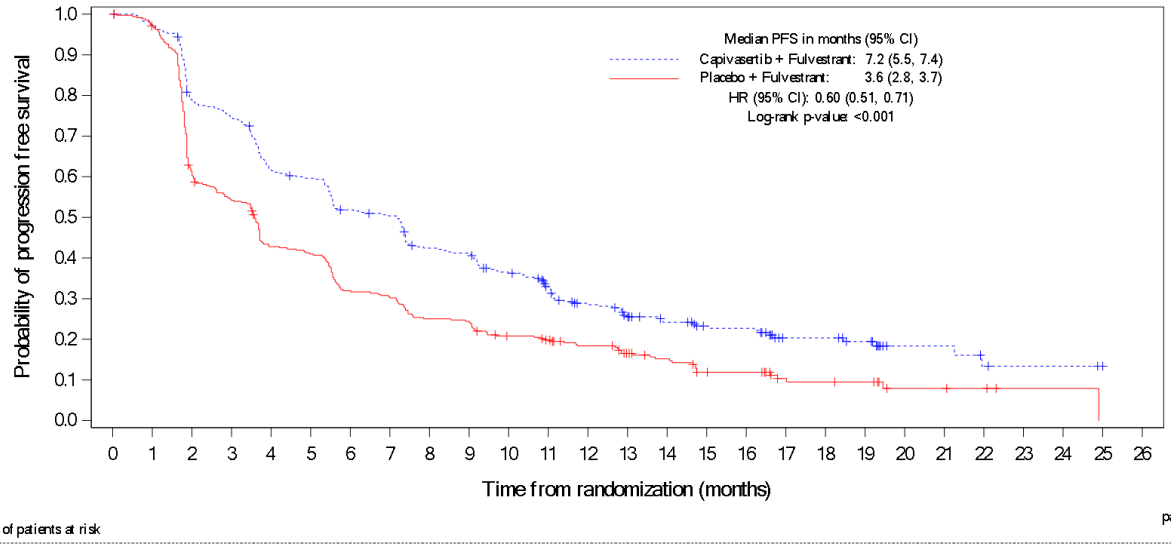
Table 47 Progression-free survival based on investigator assessments, per RECIST 1.1 at DCO1 15 August 2022, primary analysis - pivotal CAPItello-291 study (overall population and altered population)

	Overall Population		Altered Population	
	Capivasertib + Fulvestrant (N = 355)	Placebo + Fulvestrant (N = 353)	Capivasertib + Fulvestrant (N = 155)	Placebo + Fulvestrant (N = 134)
Total number of patients with events, n (%) [a]	258 (72.7)	293 (83.0)	121 (78.1)	115 (85.8)
RECIST progression	249 (70.1)	281 (79.6)	115 (74.2)	108 (80.6)
Target lesions [b]	104 (29.3)	142 (40.2)	45 (29.0)	59 (44.0)
Non-target lesions [b]	73 (20.6)	107 (30.3)	31 (20.0)	42 (31.3)
New lesions [b]	156 (43.9)	188 (53.3)	76 (49.0)	63 (47.0)
Death in the absence of progression	9 (2.5)	12 (3.4)	6 (3.9)	7 (5.2)
Median PFS (months) [c]	7.2	3.6	7.3	3.1
95% CI for median PFS [c]	5.5, 7.4	2.8, 3.7	5.5, 9.0	2.0, 3.7
PFS rate at 6 months (%) [c]	51.8	32.0	53.4	29.6
95% CI for PFS rate at 6 months [c]	46.4, 57.0	27.0, 37.0	45.1, 60.9	21.9, 37.7
PFS rate at 9 months (%) [c]	40.9	24.4	42.0	21.6
95% CI for PFS rate at 9 months [c]	35.6, 46.1	19.9, 29.1	34.0, 49.7	14.9, 29.1
PFS rate at 12 months (%) [c]	28.5	18.4	28.2	15.8
95% CI for PFS rate at 12 months [c]	23.7, 33.5	14.4, 22.8	21.2, 35.6	10.0, 22.7
Comparison between groups				
2-sided p-value [d]	< 0.001		< 0.001	

	Overall Population		Altered Population	
	Capivasertib + Fulvestrant (N = 355)	Placebo + Fulvestrant (N = 353)	Capivasertib + Fulvestrant (N = 155)	Placebo + Fulvestrant (N = 134)
Hazard ratio [e]	0.60		0.50	
95% CI for hazard ratio [e]	0.51, 0.71		0.38, 0.65	
96.50% CI for hazard ratio [e]	0.50, 0.72		-	

To the 551 PFS events contributed 530 progression events, most of them new lesions, and 21 deaths without documented progression. In the capivasertib + fulvestrant arm and the placebo + fulvestrant arm 97 (27.3%) and 60 (17.0 %) patients were censored, respectively.

Figure 13 Kaplan-Meier plot of progression-free survival based on investigator assessments, per RECIST 1.1 at DCO1 15 August 2022, primary analysis - pivotal CAPItello-291 study (overall population)



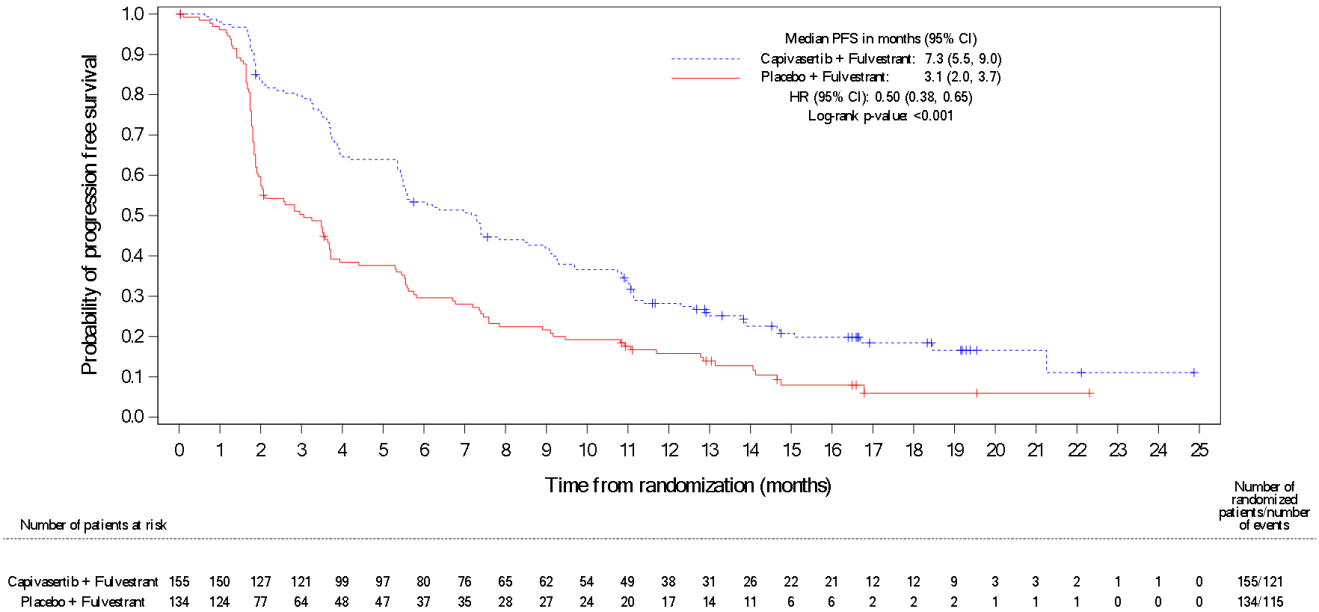
Number of patients at risk

Number of randomized patients/number of events

Capivasertib + Fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0	355/258
Placebo + Fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0	353/293

+ indicates a censored observation.
Note: Progression determined by RECIST 1.1. Does not include RECIST progression events that occur after 2 or more missed visits or death after 2 visits of baseline where the patient has no evaluable visits or does not have a baseline assessment. 2-sided p-value. Hazard ratio calculated using stratified Cox proportional hazards model. Log-rank test and Cox model were stratified by presence of 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). A hazard ratio < 1 favours capivasertib + fulvestrant.
HR = hazard ratio.

Figure 14 Kaplan-Meier plot of progression-free survival based on investigator assessments, per RECIST 1.1 at DCO1 15 August 2022, primary analysis - pivotal CAPItello-291 study (altered population)



+ indicates a censored observation.
Note: Progression determined by RECIST 1.1. Does not include RECIST progression events that occur after 2 or more missed visits or within 2 visits of baseline where the patient has no evaluable visits or does not have a baseline assessment. 2-sided p-value. Hazard ratio calculated using stratified Cox proportional hazards model. Log-rank test and Cox model were stratified by presence of liver metastases (yes vs no), and prior use of CDK4/6 inhibitors (yes vs no). A hazard ratio < 1 favours capivasertib + fulvestrant.
HR = hazard ratio.

Key secondary endpoint: Overall survival

According to the multiple testing procedure, only a small alpha was spent for the OS analysis at this data cut-off and the null hypothesis could not be rejected (spending small alpha was advised by the FDA, while originally no alpha was planned to be spent at all). Therefore, the results are exploratory only.

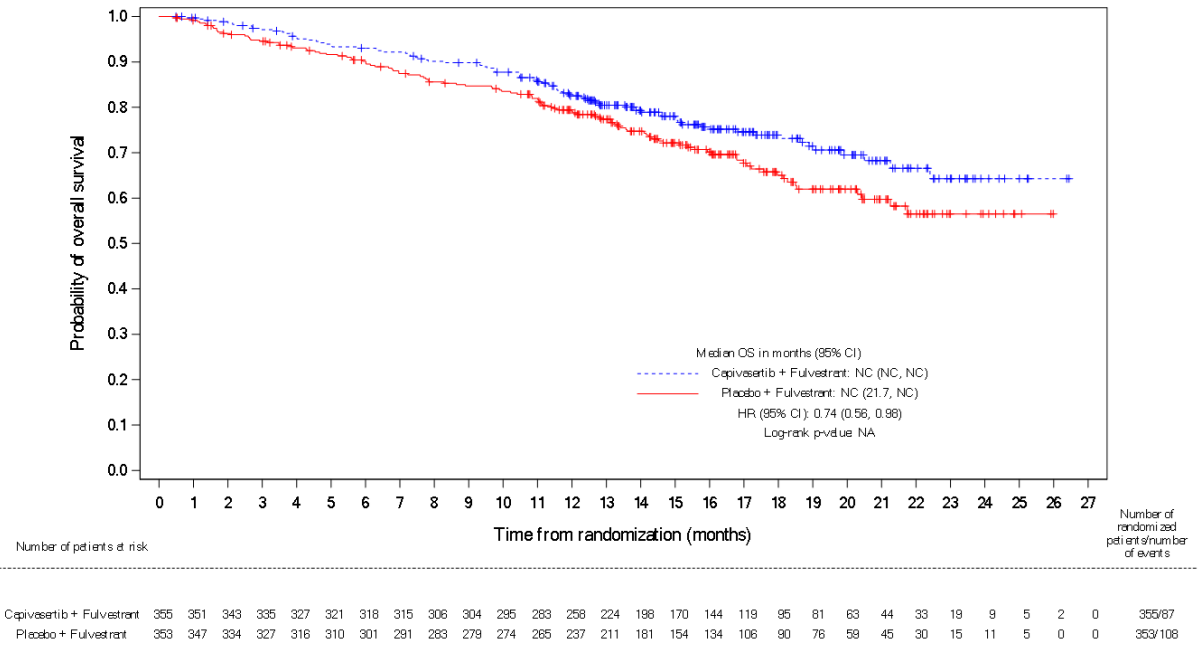
Table 48 Overall survival at DCO1 15 August 2022, secondary analysis - pivotal CAPItello-291 study (overall population)

	Capivasertib + Fulvestrant (N = 355)	**Placebo + Fulvestrant (N = 353)**
Death, n (%)	87 (24.5)	108 (30.6)
Censored patients, n (%)	268 (75.5)	245 (69.4)
Still in survival follow-up [a]	249 (70.1)	215 (60.9)
Terminated prior to death [b]	19 (5.4)	30 (8.5)
Lost to follow-up	4 (1.1)	3 (0.8)
Withdrawn consent	15 (4.2)	25 (7.1)
Discontinued study (any other specified reason for discontinuing study)	0	2 (0.6)
Death with no recorded death date	0	0
Median overall survival (months) [c]	NC	NC
95% CI for median overall survival [c]	NC, NC	21.7, NC
Overall survival rate at 18 months (%) [c]	73.9	65.0

	Capivasertib + Fulvestrant (N = 355)	Placebo + Fulvestrant (N = 353)
95% CI for overall survival rate at 18 months [c]	68.3, 78.7	58.7, 70.6
Overall survival rate at 24 months (%) [c]	64.3	56.5
95% CI for overall survival rate at 24 months [c]	55.5, 71.8	48.3, 63.9
2-sided p-value [d]	Not applicable	Not applicable
Hazard ratio [e]	0.74	
95% CI for hazard ratio [e]	0.56, 0.98	
Median (range) duration of follow-up in censored patients (months)	15.9 (0.5, 26.4)	15.4 (0.5, 26.0)

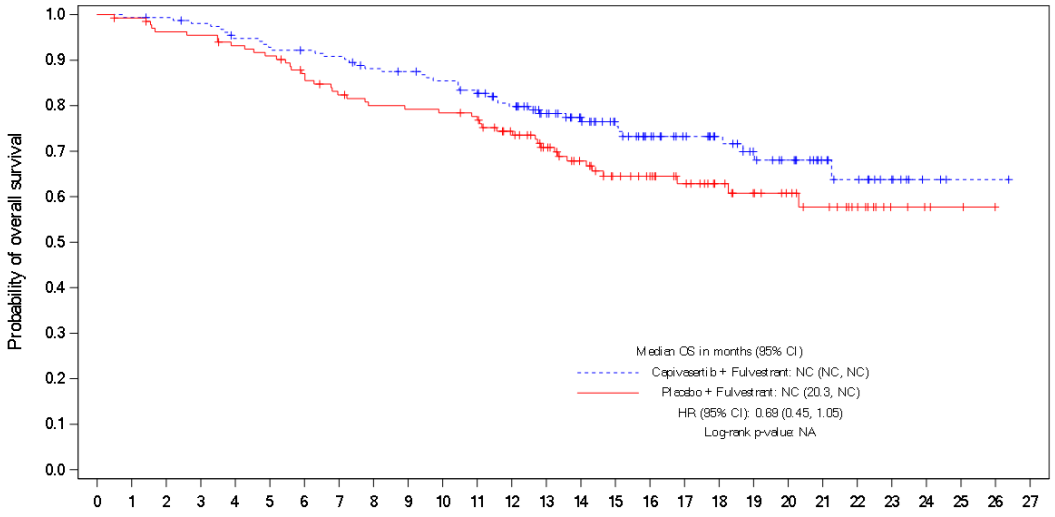
Includes patients known to be alive at data cut-off date.
Includes patients with unknown survival status or patients who were lost to follow-up.
Kaplan-Meier estimate. CI for median overall survival is derived based on Brookmeyer-Crowley method.
Stratified log-rank test.
Stratified Cox proportional hazards model. A hazard ratio < 1 favours capivasertib + fulvestrant.
Log-rank test and Cox model stratified by presence of liver metastases (yes vs no), prior use of CDK4/6 inhibitors (yes vs no).
0.01% alpha penalty assigned to the assessment of no OS detriment. Formal analysis not prespecified.

Figure 15 Kaplan-Meier plot of overall survival at DCO1 15 August 2022, secondary analysis - pivotal CAPItello-291 study (overall population)



+ indicates a censored observation.
Note: 0.01% alpha penalty assigned to the assessment of no OS detriment. Formal analysis not prespecified. Patients not known to have died at the time of analysis are censored at the last recorded date on which the patient was last known to be alive. 2-sided p-value. Hazard ratio calculated using stratified Cox proportional hazards model. Log-rank test and Cox model were stratified by presence of liver metastases (yes vs no), prior use of CDK4/6 inhibitors (yes vs no). A hazard ratio < 1 favours capivasertib + fulvestrant.
HR = hazard ratio.

Figure 16 Kaplan-Meier plot of overall survival at DCO1 15 August 2022, secondary analysis - pivotal CAPItello-291 study (altered population)



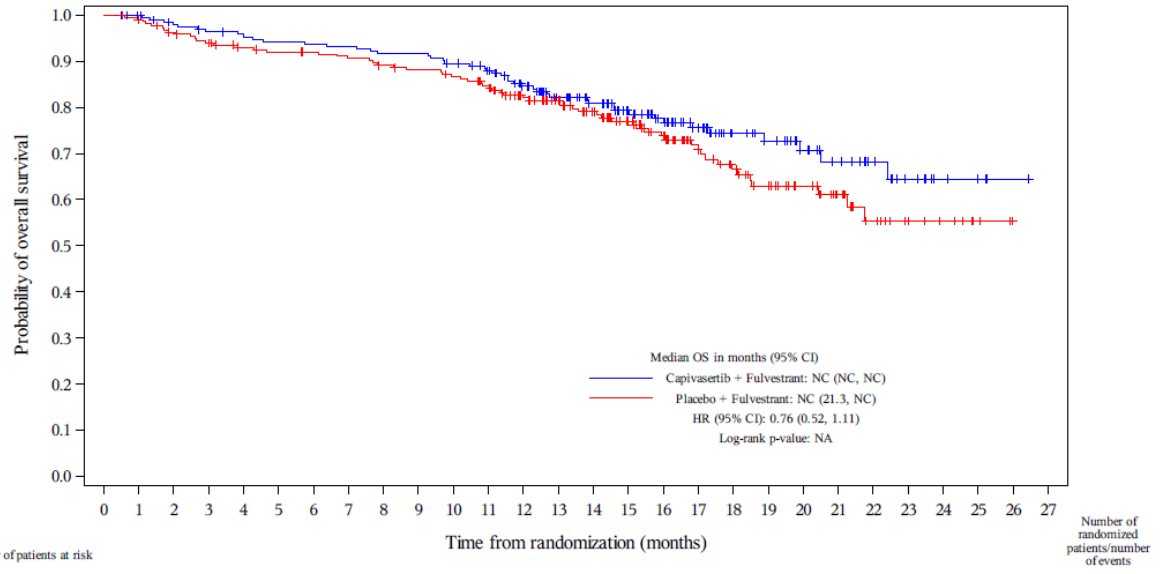
Number of patients at risk

Number of randomized patients/number of events

Capivasertib + Fulvestrant	155	154	153	150	144	141	139	137	131	129	125	121	111	96	83	71	60	53	45	37	30	18	14	8	3	1	1	0	155/41
Placebo + Fulvestrant	134	132	127	126	122	119	112	105	101	100	99	97	87	75	62	51	46	39	31	26	22	18	13	5	3	2	0	0	134/46

+ indicates a censored observation.
Note: 0.01% alpha penalty assigned to the assessment of no OS detriment. Formal analysis not prespecified. Patients not known to have died at the time of analysis are censored at the last recorded date on which the patient was last known to be alive. 2-sided p-value. Hazard ratio calculated using stratified Cox proportional hazards model. Log-rank test and Cox model were stratified by prior use of CDK4/6 inhibitors (yes vs no). A hazard ratio < 1 favours capivasertib + fulvestrant.
HR = hazard ratio.

Figure 17 Kaplan-Meier plot of overall survival at DCO1 15 August 2022, exploratory analysis - pivotal CAPItello-291 study (non-altered population)



Number of patients at risk

Number of randomized patients/number of events

Capivasertib + Fulvestrant	200	197	190	185	183	180	179	178	175	175	170	162	147	128	115	99	84	66	50	44	33	26	19	11	6	4	1	0	200/46
Placebo + Fulvestrant	219	215	207	201	194	191	189	186	182	179	175	168	150	136	119	103	88	67	59	50	37	27	17	10	8	3	0	0	219/62

+ indicates a censored observation.
Note: Patients not known to have died at the time of analysis are censored at the last recorded date on which the patient was last known to be alive. 2-sided p-value. Hazard ratio calculated using stratified Cox proportional hazards model. Log-rank test and Cox model were stratified by presence of liver metastases (yes vs no), prior use of CDK4/6 inhibitors (yes vs no). A hazard ratio < 1 favours capivasertib + fulvestrant.
HR = hazard ratio.

Other secondary endpoints

Overall response rate

Formal tests for the objective response rates is planned for future analyses. Exploratory analyses for both primary populations were presented and best objective response rate by INV are reported for the overall population and for the *PIK3CA/AKT1/PTEN altered population*.

Table 49 Overall response rate

Descriptive statistics and estimate variability (ORR)	Treatment group	Overall Population		Altered Population	
		C+F	P+F	C+F	P+F
	Number of subjects [g]	N=310	N=320	N=132	N=124
	Number (%) of patients with response	71 (22.9)	39 (12.2)	38 (28.8)	12 9.7)

In the *Known non altered population*, ORR was 17.1 % for capivasertib+fulvestrant and 14.5 % for placebo+fulvestrant.

Duration of response – based on small numbers - was similar in both arms (9.8 vs 8.4 months and 9.4 vs 8.6 months for capivasertib+fulvestrant and placebo+fulvestrant in the Overall population and PIK3CA/AKT1/PTEN altered population, respectively).

PFS2

Table 50 Time from randomisation to second progression or death at DCO1 15 August 2022, secondary analysis - pivotal CAPItello-291 study (overall population and altered population)

	Overall Population		**Altered Population**	
	Capivasertib + Fulvestrant (N = 355)	**Placebo + Fulvestrant (N = 353)**	**Capivasertib + Fulvestrant (N = 155)**	**Placebo + Fulvestrant (N = 134)**
Total number of patients with events, n (%) [a]	176 (49.6)	207 (58.6)	79 (51.0)	87 (64.9)
Second progression	132 (37.2)	155 (43.9)	57 (36.8)	62 (46.3)
Death in the absence of second progression	44 (12.4)	52 (14.7)	22 (14.2)	25 (18.7)
Censored patients, n (%) [b]	179 (50.4)	146 (41.4)	76 (49.0)	47 (35.1)
Median PFS2 (months) [c]	14.7	12.5	15.5	10.8
95% CI for median PFS 2 [c]	13.6, 16.4	11.3, 13.4	13.2, 17.6	8.1, 12.7
PFS2 rate at 6 months (%) [c]	85.3	77.8	86.7	72.2
95% CI for PFS2 rate at 6 months [c]	81.1, 88.7	72.9, 82.0	80.2, 91.2	63.5, 79.2
PFS2 rate at 9 months (%)[c]	73.4	63.5	76.6	55.1
95% CI for PFS2 rate at 9 months [c]	68.3, 77.9	58.0, 68.5	68.9, 82.6	45.9, 63.3
PFS2 rate at 12 months (%) [c]	62.8	52.2	64.4	44.6
95% CI for PFS 2 rate at 12 months [c]	57.2, 67.9	46.5, 57.6	56.0, 71.6	35.6, 53.2
2-sided p-value [d]	< 0.001		< 0.001	
Hazard ratio [e]	0.70		0.52	
95% CI for hazard ratio [e]	0.57, 0.86		0.38, 0.71	
Median (range) duration of follow-up in censored patients (months)	13.1 (0.0, 25.0)	12.9 (0.0, 24.9)	13.8 (0.0, 24.9)	13.0 (0.0, 24.0)

Progression events determined by investigator assessment subsequent to the first subsequent therapy or death.
Patients alive and for whom a second disease progression has not been observed censored at the date last known alive and without a second disease progression.
Calculated using the Kaplan-Meier technique.

Calculated using stratified log-rank test.
Calculated using stratified Cox proportional hazards model. A hazard ratio < 1 favours capivasertib + fulvestrant. Log-rank test and Cox model stratified by presence of liver metastases (yes vs no), prior use of CDK4/6 inhibitors (yes vs no).

For the 'Known Non-altered Population' median PFS2 is reported with 13.9 vs 13.1 months (HR 0.95; 95% CI: 0.70, 1.29) for capivasertib+fulvestrant and placebo+fulvestrant, respectively.

Patient-reported Outcomes / Health-related Quality of Life (HRQoL)

EORTC QLQ-C30, EORTC QLQ-BR23 and EQ-5D PRO questionnaires were used for the evaluation of HRQoL. Overall, presented data (data not shown) show no clinically relevant changes in quality of life between the control and the experimental arm (neither in the overall population nor in the altered population).

- **Ancillary analyses**

Sensitivity analyses of PFS

Several sensitivity analyses were provided. Importantly, a BICR assessment was performed for the full population.

Further sensitivity analyses for evaluation time bias and for attrition bias were performed: In the sensitivity analysis for evaluation time bias, the midpoint between the time of progression and the previous evaluable RECIST v1.1 assessment was analysed. In the sensitivity analysis for attrition bias, patients who progressed or died in the absence of progression immediately following 2 or more missed assessments were included. Patients who took subsequent therapy prior to progression or death were censored at their last evaluable assessment prior to taking the subsequent therapy.

A further sensitivity analysis was conducted to assess for the potential impact of COVID-19 deaths on PFS. There was no impact of COVID-19 deaths on PFS. One patient in the placebo + fulvestrant arm died due to COVID-19.

Table 51 Progression-free survival sensitivity analyses (*overall population* and PIK3CA/AKT1/PTEN altered population)

Group	N	Number (%) of patients with events	Median (months) [a]	Comparison between groups		
				Hazard ratio [b, c]	95% CI [b, c]	2-sided p-value [c, d]
Overall Population						
Evaluation-time bias [e]						
Capivasertib + fulvestrant	355	258 (72.7)	6.3	0.60	0.51, 0.71	< 0.001
Placebo + fulvestrant	353	293 (83.0)	2.7			
Attrition bias [f]						
Capivasertib + fulvestrant	355	265 (74.6)	7.2	0.61	0.52, 0.72	< 0.001
Placebo + fulvestrant	353	296 (83.9)	3.6			
Ascertainment bias (BICR) [g]						
Capivasertib + fulvestrant	355	215 (60.6)	7.3	0.61	0.50, 0.73	< 0.001
Placebo + fulvestrant	353	238 (67.4)	3.7			
Altered Population						
Evaluation-time bias [e]						
Capivasertib + fulvestrant	155	121 (78.1)	6.4	0.50	0.39, 0.66	< 0.001
Placebo + fulvestrant	134	115 (85.8)	2.4			

Attrition bias [f]						
Capivasertib + fulvestrant	155	121 (78.1)	7.3	0.51	0.39, 0.66	< 0.001
Placebo + fulvestrant	134	117 (87.3)	3.3			
Ascertainment bias (BICR) [g]						
Capivasertib + fulvestrant	155	98 (63.2)	7.3	0.51	0.38, 0.68	< 0.001
Placebo + fulvestrant	134	88 (65.7)	3.3			

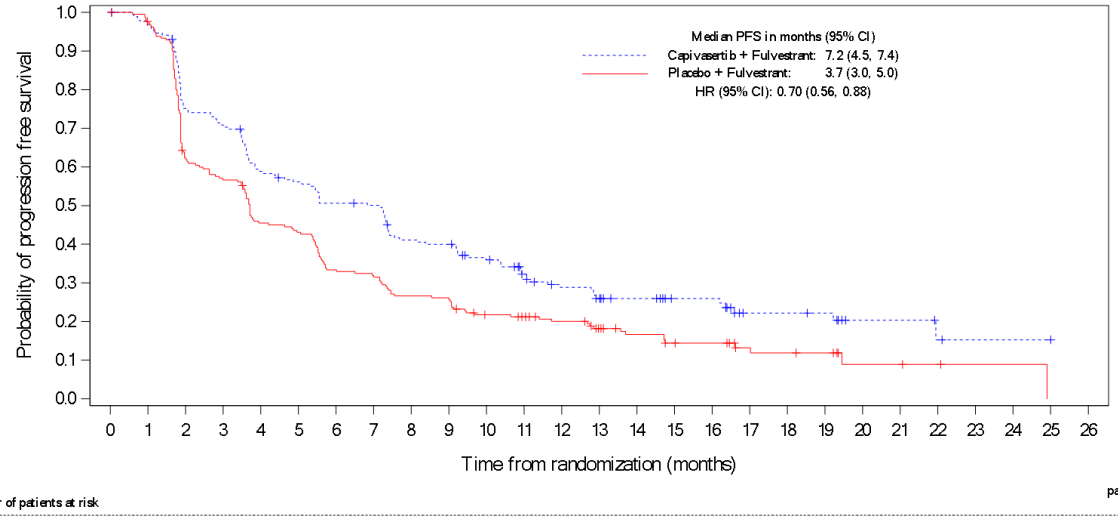
[a] Kaplan-Meier estimate.
b Cox proportional hazards model.
c Log-rank test and Cox model were stratified by presence of liver metastases (yes vs no), prior use of CDK4/6 inhibitors (yes vs no).
d Stratified log-rank test.
e The midpoint between the time of progression and the previous evaluable RECIST v1.1 assessment was analysed.
f Patients who progressed or died in the absence of progression immediately following 2 or more missed assessments were included. Patients who took subsequent therapy prior to progression or death were censored at their last evaluable assessment prior to taking the subsequent therapy.
g Blinded Independent Central Review data based upon RECIST v1.1 was used. Source: Table 14.2.1.5 and Table 14.2.1.18.

Concordance rates for PFS between investigator and central review

Disagreements between investigator and central reviews of RECIST v1.1 progression were presented for each treatment group (data not shown).

Exploratory analyses: PFS in the non-altered Population

Figure 18 Kaplan-Meier plot of progression-free survival based on investigator assessments, per RECIST 1.1 at DCO1 15 August 2022, exploratory analysis - pivotal CAPItello-291 study (non-altered population)



Number of patients at risk

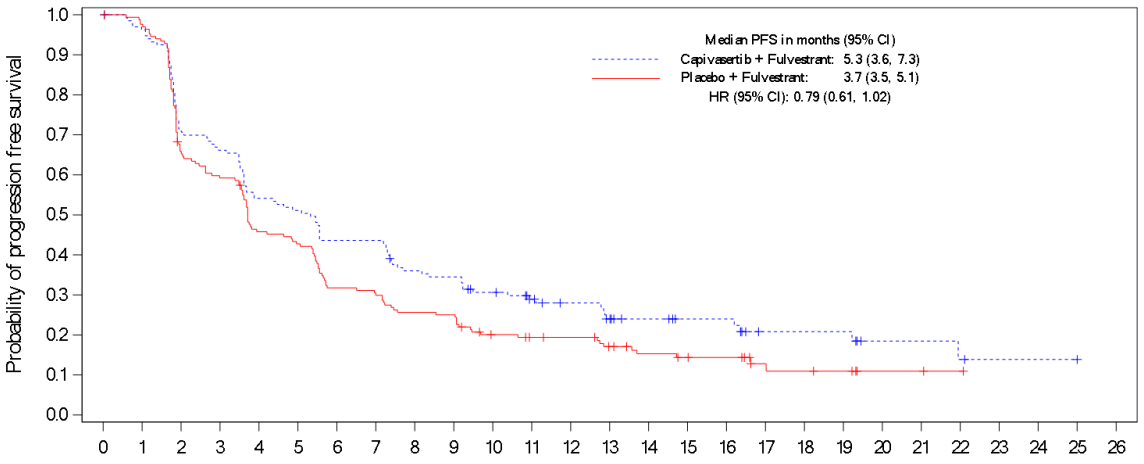
Number of randomized patients/number of events

Capivasertib + Fulvestrant	200	180	139	131	108	102	92	90	73	71	61	49	40	33	29	22	22	13	13	12	5	5	3	1	1	1	0	200/137
Placebo + Fulvestrant	219	205	130	118	94	89	69	65	55	54	42	39	34	27	22	18	17	10	9	8	3	3	2	1	1	0	0	219/178

+ indicates a censored observation.
Note: Progression determined by RECIST 1.1. Does not include RECIST progression events that occur after 2 or more missed visits or within 2 visits of baseline where the patient has no evaluable visits or does not have a baseline assessment. Hazard ratio calculated using stratified Cox proportional hazards model. Log-rank test and Cox model were stratified by presence of liver metastases (yes vs no), and prior use of CDK4/6 inhibitors (yes vs no). A hazard ratio < 1 favours capivasertib + fulvestrant. Non-altered Population includes patients with unknown biomarker results.
HR = hazard ratio.
Source: Figure 14.2.1.24, CAPItello-291 CSR, Module 5.3.5.1.

Exploratory analysis further divided the *Non-altered Population* into the *Known Non-altered Population* and the *No Result Population* depending on the fact if non-alteration status was confirmed by a valuable laboratory finding.

Figure 19 Kaplan-Meier plot of progression-free survival based on investigator assessments, per RECIST 1.1 at DCO1 15 August 2022, exploratory analysis - pivotal CAPItello-291 study (known non-altered population)



Number of patients at risk

Number of randomized patients/number of events

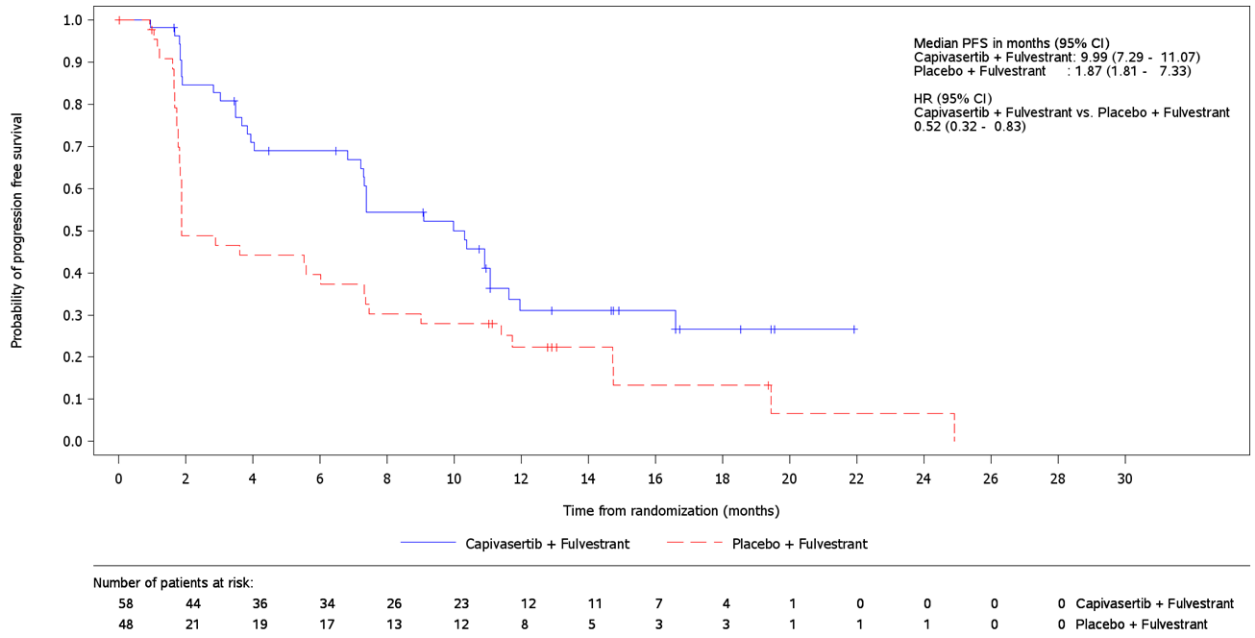
Capivasertib + Fulvestrant	142	128	95	88	72	68	58	58	47	45	38	32	28	22	18	15	15	9	9	9	4	4	3	1	1	1	0	142/103
Placebo + Fulvestrant	171	163	109	98	75	70	52	49	42	41	30	27	26	21	17	15	14	7	6	5	2	2	1	0	0	0	0	171/141

+ indicates a censored observation.
Note: Progression determined by RECIST 1.1. Does not include RECIST progression events that occur after 2 or more missed visits or within 2 visits of baseline where the patient has no evaluable visits or does not have a baseline assessment. Hazard ratio calculated using stratified Cox proportional hazards model. Log-rank test and Cox model were stratified by presence of liver metastases (yes vs no), and prior use of CDK4/6 inhibitors (yes vs no). A hazard ratio < 1 favours capivasertib + fulvestrant.
HR = hazard ratio.
Source: Figure 14.2.1.23, CAPItello-291 CSR, Module 5.3.5.1.

Median PFS by BICR is reported with 3.9 vs 3.7 months (HR 0.85, 95% CI 0.65, 1.12) for capivasertib+fulvestrant and placebo+fulvestrant, respectively.

In the *No Result Population*, a reduction in the risk of progression in favour of capivasertib + fulvestrant was reported with a hazard ratio of 0.52; 95% CI: 0.32, 0.83.

Figure 20 Kaplan-Meier plot of progression-free survival based on investigator assessments, per RECIST 1.1 at DCO1 15 August 2022, post hoc exploratory analysis - pivotal CAPItello-291 study (no result population)

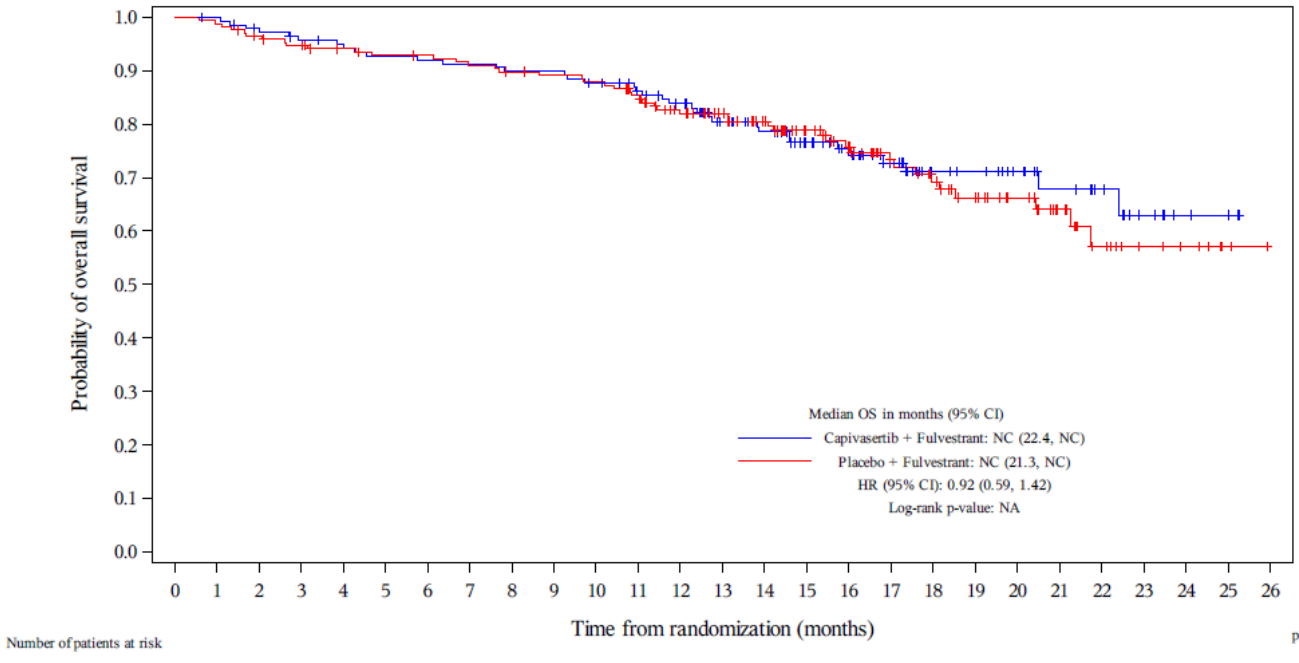


+ indicates a censored observation.
Note: Progression determined by RECIST 1.1. Does not include RECIST progression events that occur after 2 or more missed visits or death after 2 visits of baseline where the patient has no evaluable visits or does not have a baseline assessment. Hazard ratio calculated using stratified Cox proportional hazards model. Hazard ratio < 1 favours capivasertib + fulvestrant. Cox model stratified by prior use of CDK4/6 inhibitors (yes vs no).
HR = hazard ratio.
Source: IEMT083 HLR0024.1, CAPItello-291 CSR, Module 5.3.5.1.

Exploratory analyses Overall Survival by subgroup

The risk of death in favour of capivasertib + fulvestrant was in the entire Non-altered Population (hazard ratio: 0.76; 95% CI: 0.52, 1.11).

Figure 21 Kaplan-Meier plot of overall survival at DCO1 15 August 2022, exploratory analysis - pivotal CAPItello-291 study (known non-altered population)

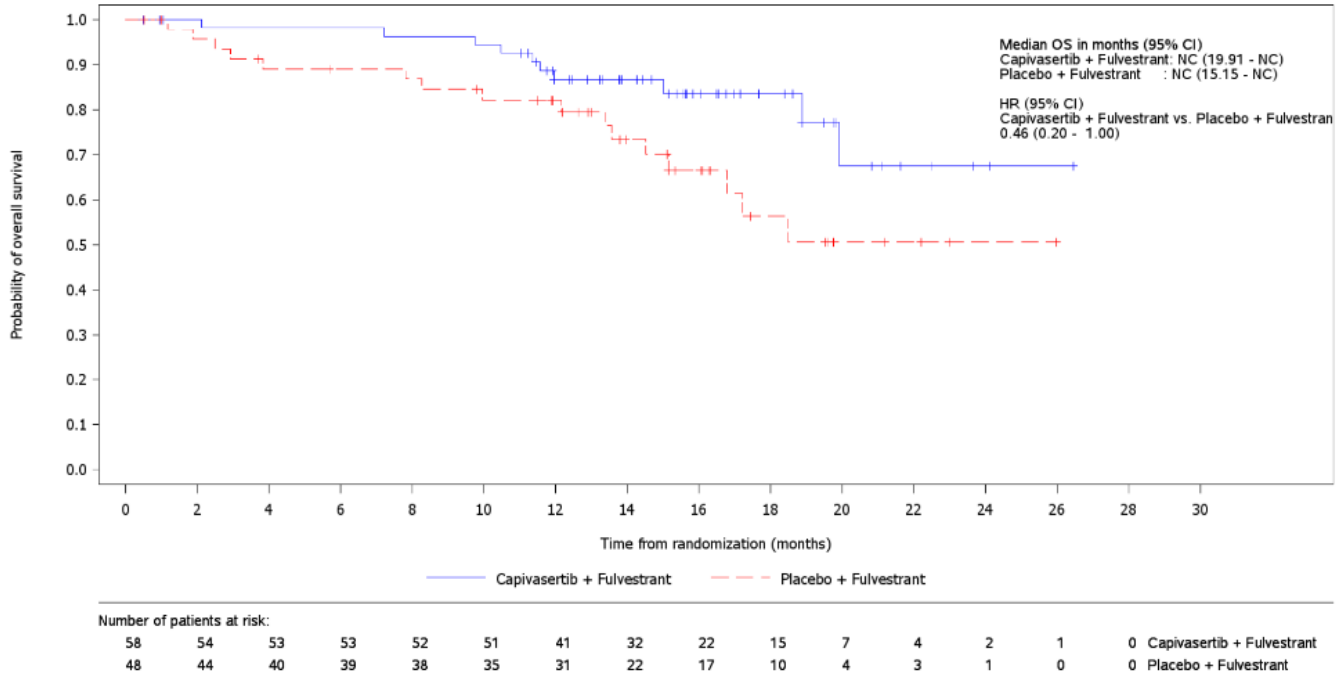


Number of patients at risk

																										Number of randomized patients/number of events
Capivasertib + Fulvestrant	142	141	136	132	130	127	126	125	123	123	119	112	106	90	83	70	62	49	35	33	26	20	15	8	4	3	0	142/36
Placebo + Fulvestrant	171	169	163	159	154	151	150	147	144	142	140	133	119	109	97	82	71	55	49	41	33	23	14	9	7	2	0	171/46

+ indicates a censored observation.
Note: Patients not known to have died at the time of analysis are censored at the last recorded date on which the patient was last known to be alive. 2-sided p-value. Hazard ratio calculated using stratified Cox proportional hazards model. Log-rank test and Cox model were stratified by prior use of CDK4/6 inhibitors (yes vs no). A hazard ratio < 1 favours capivasertib + fulvestrant.
HR = hazard ratio.

Figure 22 Kaplan-Meier plot of overall survival at DCO1 15 August 2022, post hoc exploratory analysis - pivotal CAPItello-291 study (no result population)



+ indicates a censored observation.
Note: Patients not known to have died at the time of analysis are censored at the last recorded date on which the patient was last known to be alive. A hazard ratio < 1 favours capivasertib + fulvestrant. Hazard ratio calculated using stratified Cox proportional hazards model. Cox model unstratified following the pooling strategy.
HR = hazard ratio.
Source: IEMT083 HLR0024.2, Appendix 2.7.3.6.1, Module 5.3.5.3.

Subgroup analysis by prior use of CDK4/6 inhibitors

In patients with prior CDK4/6 inhibitor use, median PFS was 5.5 months in the capivasertib + fulvestrant arm, compared to 2.6 months in the placebo + fulvestrant arm (hazard ratio: was 0.59; 95% CI: 0.48, 0.72).

In patients with no prior CDK4/6 inhibitor use, median PFS was 10.9 months in the capivasertib + fulvestrant arm, compared to 7.2 months in the placebo + fulvestrant arm (hazard ratio was 0.64; 95% CI: 0.45, 0.90).

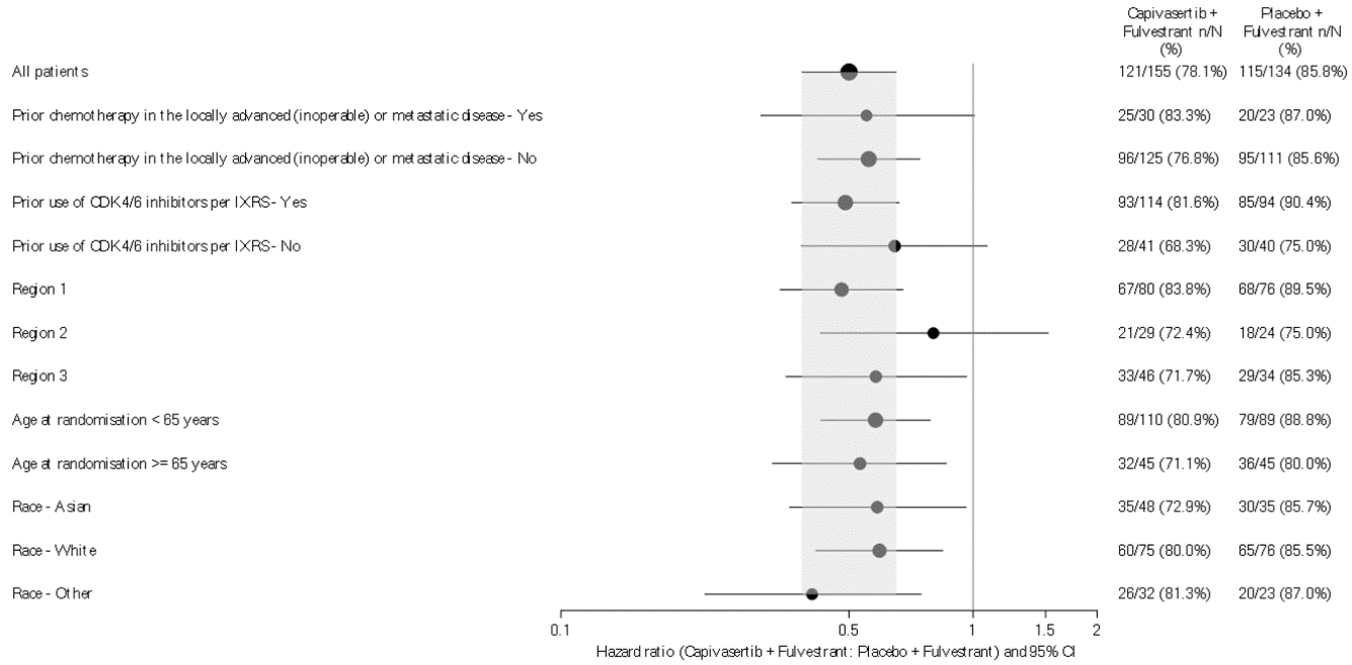
Strata and further subgroups

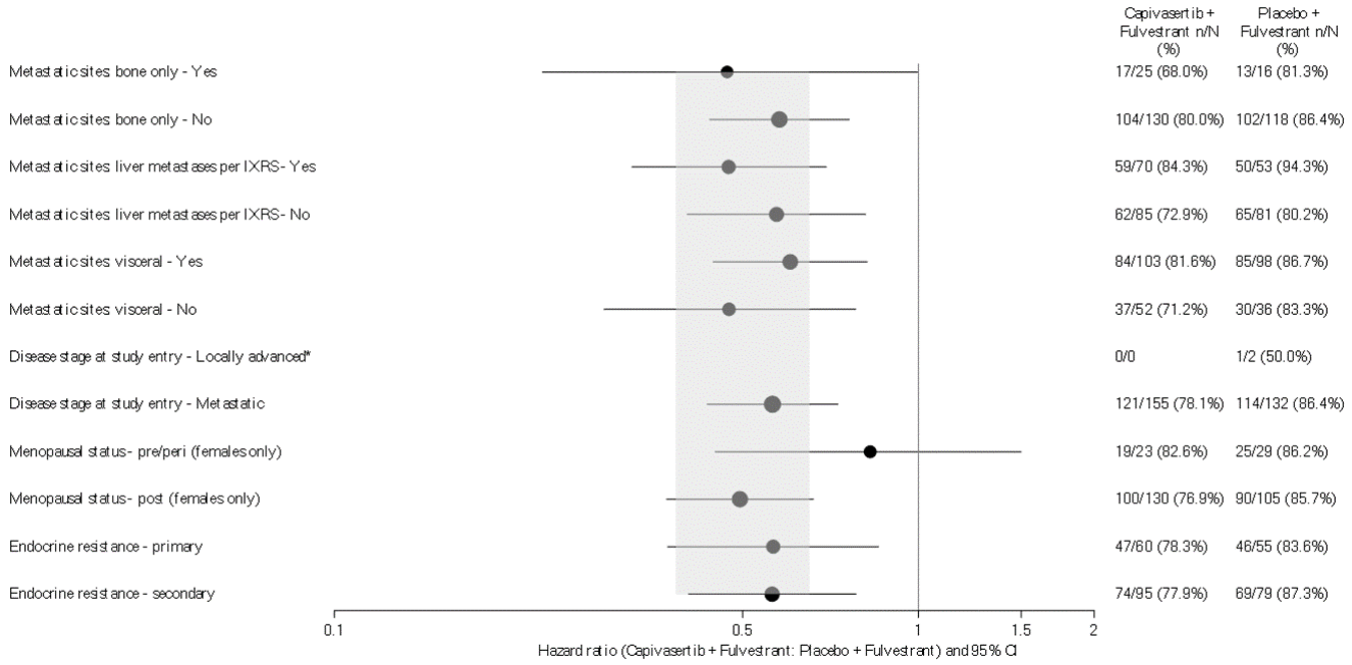
Subgroup analyses addressed the homogeneity of treatment effects for the strata - regions, prior use of CDK 4/6 inhibitors and presence of liver metastases - and for relevant subgroups, under which are menopausal status, type of metastases or prior use of chemotherapy, number of treatment lines, and importantly for different types of mutational status. Forest plots were provided for the overall population as well as the PIK3CA/AKT1/PTEN altered population.

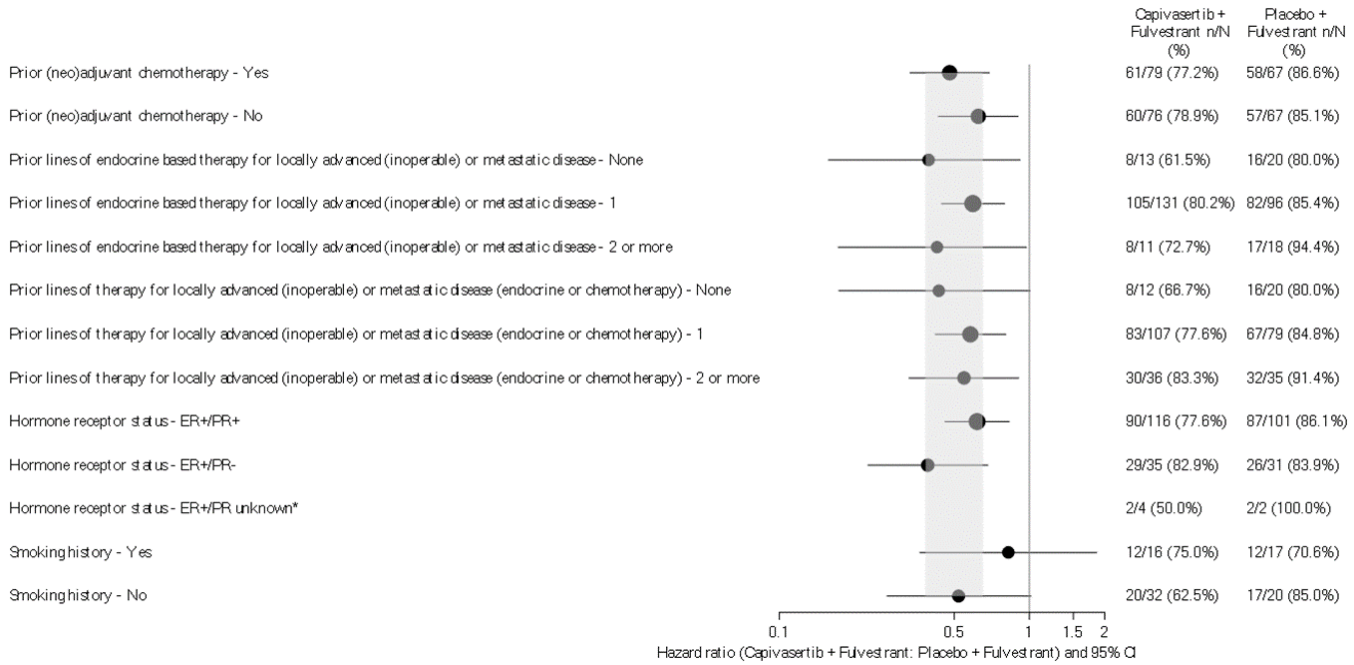
It is observed that the point estimate is uniformly in favour of capivasertib+fulvestrant. In the overall population, effect sizes are smaller and 95% CI cross the 1 for the subgroups region 2, pre/perimenopausal state, and smoking history 'yes'. All these subgroups are small (below 100 patients per arm) and CI are wide.

Effect size is larger in subgroups of patients without visceral metastases and no prior endocrine based treatment. The same observations were made for the PIK3CA/AKT1/PTEN altered population.

Figure 23 Forest plot of progression-free survival based on investigator assessments, per RECIST 1.1 at DCO1 15 August 2022, by subgroup - pivotal CAPItello-291 study (altered population)







Size of circle is proportional to the number of events. Grey band represents the 95% confidence interval for the overall (all patients) hazard ratio.
Note: Progression determined by RECIST 1.1. Hazard ratio < 1 implies a lower risk of progression on capivasertib + fulvestrant. Cox proportional hazards model including treatment term only was fitted for each subgroup level as factor. 'All patients' analysis present primary analysis results for the Altered Population. Progression includes deaths in the absence of RECIST progression. Does not include RECIST progression events baseline that occur after 2 or more missed visits or death after 2 visits of baseline where the patient has no evaluable visits or does not have a baseline assessment. Race 'other' includes Black or African American, and Israel; Native Hawaiian or Other Pacific Islander and American Indian or Alaska Native. Region 1: United States, Canada, Western Europe, Australia, and Israel; Region 2: Latin America, Eastern Europe, and Russia; Region 3: Asia.
* Hazard ratio and CI not calculated due to insufficient number of events.

<u>PIK3CA/AKT1/PTEN altered population further by-gene analysis</u>

For the PIK3CA/AKT1/PTEN altered population, further by-gene analysis of PFS by AKT1, PIK3CA and/or PTEN alteration status was also conducted post hoc. In respect to the evaluation of the clinical validity of the biomarker these by-gene analyses are important to address at least the effects of the more frequent gene alterations.

The following by-gene analyses were performed and the Kaplan-Meier plots were presented:

- *AKT1* only (hazard ratio: 0.51, 95% CI: 0.22, 1.12).
- *PIK3CA* only (hazard ratio: 0.51, 95% CI: 0.37, 0.70).
- *PTEN* only (hazard ratio: 0.43; 95% CI, 0.21, 0.88).
- *AKT1* independent (i.e., irrespective of the presence) of *PIK3CA*/*PTEN* (hazard ratio: 0.55, 95% CI: 0.26, 1.17).
- *PIK3CA* independent of *AKT1*/*PTEN* (hazard ratio: 0.51, 95% CI: 0.37, 0.69).
- *PTEN* independent of *AKT1*/*PIK3CA* (hazard ratio: 0.45, 95% CI: 0.24, 0.84).
- *PIK3A* and/or *AKT1* independent of *PTEN* (hazard ratio: 0.50, 95% CI: 0.38, 0.66).
- *PIK3CA* and/or *AKT1* without (i.e., in the absence of) *PTEN* (hazard ratio: 0.50, 95% CI: 0.38, 0.67).

Results (HR) for these by-gene analyses of PFS for AKT1, PIK3CA and/or PTEN alteration status are consistent with the result for the PIK3CA/AKT1/PTEN altered population. The subgroups of *AKT1* mutation only and PTEN mutation only are very small.

- **Summary of main efficacy results.**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 52 Summary of efficacy for trial D3615C00001 (CAPItello-291)

Title: 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			
Study identifier	Study code: D3615C00001 EudraCT number: 2019-003629-78		
Design	Phase III, double-blind, placebo-controlled, parallel-group, randomised, multicentre study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Ongoing Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Capivasertib + Fulvestrant (C+F)		355 patients were randomised to receive: • 400 mg capivasertib (2 tablets of 200 mg) orally, twice daily (BD) (total daily dose 800 mg) on Days 1 to 4 in each week of a 28-day treatment cycle, and • 500 mg fulvestrant via intramuscular injection on Day 1 of Weeks 1 and 3 of Cycle 1, and then on Day 1, Week 1 of each cycle thereafter.
	Placebo + Fulvestrant (P+F)		353 patients were randomised to receive: • Placebo (2 tablets) orally, BD on Days 1 to 4 in each week of a 28-day treatment cycle, and • 500 mg fulvestrant via intramuscular injection on Day 1 of Weeks 1 and 3 of Cycle 1, and then on Day 1, Week 1 of each cycle thereafter.
	Study treatment was continued until disease progression unless there was evidence of unacceptable toxicity, or if the patient requested to stop the study treatment.		
Endpoints and definitions	Dual primary endpoint	PFS	Progression-free survival (PFS) in the capivasertib + fulvestrant arm relative to the placebo + fulvestrant arm in the *'Overall population'* and in the *'Altered Population'*. 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.
	Key secondary endpoint	OS	Overall survival (OS) in the capivasertib + fulvestrant arm relative to the placebo + fulvestrant arm in the '*Overall population'* and in the '*Altered Population*'. OS is length of time from randomisation until the date of death due to any cause.

	Secondary endpoint	ORR	Overall response rate (ORR) in the capivasertib + fulvestrant arm relative to the placebo + fulvestrant arm in the *overall population* and in the Altered Population. ORR is defined as the percentage of patients with at least one complete response or partial response per RECIST v1.1, as assessed by the investigator at the local site.

Database lock	03 October 2022				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	*Overall Population*: All patients randomised into the study, excluding patients randomised in China after the global cohort last patient first visit. *Altered Population*: Patients in the *overall population* with a *PIK3CA/AKT1/PTEN*-altered tumour determined by central testing. At the data cut-off, the median duration of follow-up in the *overall population* (defined as time to censoring or death) was 14.9 months in the C+F arm and 14.3 months in the P+F arm.				
Descriptive statistics and estimate variability (PFS)	Treatment group	Overall Population		Altered Population	
		C+F	P+F	C+F	P+F
	Number of subjects	N=355	N=353	N=155	N=134
	Total number of patients with PFS events, n (%) [a]	258 (72.7)	293 (83.0)	121 (78.1)	115 (85.8)
	Median PFS (months) [b]	7.2	3.6	7.3	3.1
	95% CI for median PFS [b]	5.5, 7.4	2.8, 3.7	5.5, 9.0	2.0, 3.7
Effect estimate per comparison (PFS)	Dual Primary Endpoint: PFS in the	Comparison groups	C+F vs P+F		
		2-sided p-value [c]	< 0.001		
		Hazard ratio [d]	0.60		
		95% CI for hazard ratio [d]	0.51, 0.71		
	Dual Primary Endpoint: PFS in the *'Altered Population'*	Comparison groups	C+F vs P+F		
		2-sided p-value [c]	< 0.001		
		Hazard ratio [d]	0.50		
		95% CI for hazard ratio [d]	0.38, 0.65		
Analysis description	**Subgroup Analysis**				

Analysis population and time point description	'*Non-altered Population*': Patients in the *overall population* excluding patients with a *PIK3CA/AKT1/PTEN*-altered tumour determined by central testing (pre-specified exploratory population). '*Known Non-altered Population*': Patients in the Non altered Population excluding those without a valid central test result (pre-specified exploratory population). '*No Result Population*': Patients in the Non altered Population without a valid central test result (post hoc exploratory population).						
Descriptive statistics and estimate variability (PFS)	Treatment group	Non-altered Population		Known Non-altered Population		No Result Population	
		C+F	P+F	C+F	P+F	C+F	P+F
	No of subjects	N=200	N=219	N=142	N=171	N=58	N=48
	Median PFS (months) [b]	7.2	3.7	5.3	3.7	10.0	1.9
	95% CI for median PFS [b]	4.5, 7.4	3.0, 5.0	3.6, 7.3	3.5, 5.1	7.3, 11.1	1.8, 7.3
Effect estimate per comparison (PFS)	Prespecified Exploratory Endpoint: PFS in the	Comparison groups		C+F vs P+F			
		Hazard ratio [d]		0.70			
		95% CI for hazard ratio [d]		0.56, 0.88			
	Prespecified Exploratory Endpoint: PFS in the Known Non-altered Population	Comparison groups		C+F vs P+F			
		Hazard ratio [d]		0.79			
		95% CI for hazard ratio [d]		0.61, **1.02**			
	Posthoc Exploratory Endpoint: PFS in the No Result Population	Comparison groups		C+F vs P+F			
		Hazard ratio [d]		0.52			
		95% CI for hazard ratio [d]		0.32, 0.83			

Analysis description	**Secondary Analysis**				
Analysis population and time point description	Overall Population Altered Population				
Descriptive statistics and estimate variability (OS)	Treatment group	Overall Population		Altered Population	
		C+F	P+F	C+F	P+F
	Number of subjects	N=355	N=353	N=155	N=134
	Death, n (%)	87 (24.5)	108 (30.6)	41 (26.5)	46 (34.3)
Effect estimate per comparison (OS)	Secondary Endpoint: OS in the *overall population* [e]	Comparison groups	C+F vs P+F		

		Hazard ratio [f]	0.74		
		95% CI for hazard ratio [f]	0.56, 0.98		
	Secondary Endpoint: OS in the *altered population* [e]	Comparison groups	C+F vs P+F		
		Hazard ratio [f]	0.69		
		95% CI for hazard ratio [f]	0.45, 1.05		
Descriptive statistics and estimate variability (ORR)	Treatment group	Overall Population		Altered Population	
		C+F	P+F	C+F	P+F
	Number of subjects [g]	N=310	N=320	N=132	N=124
	Number (%) of patients with response	71 (22.9)	39 (12.2)	38 (28.8)	12 (9.7)

Notes

a Does not include RECIST progression events that occur after 2 or more missed visits or death after 2 visits of baseline where the patient has no evaluable visits or does not have a baseline assessment.

b Kaplan-Meier estimate.

c Stratified log-rank test.

d Stratified Cox proportional hazards model. A hazard ratio < 1 favours capivasertib + fulvestrant. For the Overall Population, the log-rank test and Cox model are stratified by presence of 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). For the Altered Population, Non-altered Population, and Known Non-altered Population, the log rank test and Cox model are stratified by presence of liver metastases (yes vs no), and prior use of CDK4/6 inhibitors (yes vs no). For the No Result Population, the Cox model is stratified by prior use of CDK4/6 inhibitors (yes vs no).

e 0.01% alpha penalty assigned to the assessment of no OS detriment. Formal analysis not prespecified.

f Stratified Cox proportional hazards model. A hazard ratio < 1 favours capivasertib + fulvestrant.

g Number of patients with measurable disease at baseline in treatment group.

2.6.5.3. Clinical studies in special populations

According to the CAPITELLO 291 baseline characteristics >30% of patients were 65 years and older.

Table 53 Age distribution for older subjects (safety population)

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Phase III trials [a]	91/355	24/355	0/355
Non-controlled trials [b]	114/597	30/597	1/597

[b] CAPItello-291 study.

[c] Single-arm uncontrolled studies: D3610C00001; D3610C00002; D3610C00003; D3610C00004; D3610C00007; D3614C00002; D3614C00005; D3614C00007; D3618C00002; D361DC00001 (open-label Phase Ib part). D3610C00002 (BEECH) was included as a non-controlled trial as Part A was not a randomised controlled trial.

Patients exposed to capivasertib are presented. Ongoing blinded studies are not included.

DCO of 01 March 2023 for the Investigator's Brochure.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Scientific rationale for testing of the PIK3CA/AKT1/PTEN alteration status

Mechanism of action:

Capivasertib is a potent, selective inhibitor of the kinase activity of all 3 isoforms of serine/threonine kinase AKT (AKT1, AKT2 and AKT3). AKT is a pivotal node in the phosphatidylinositol 3-kinase (PI3K) signalling cascade regulating multiple cellular processes including cellular survival, proliferation, cell cycle, metabolism, gene transcription and cell migration. AKT activation in tumours is a result of upstream activation from other signalling pathways, mutations of AKT, loss of phosphatase and tensin homolog (PTEN) function and mutations in the catalytic subunit of PI3K (PIK3CA).

In vivo, monotherapy, capivasertib inhibits growth of human cancer xenograft models representative of different tumour types including ER+ and triple negative breast cancer models with PIK3CA, AKT1 mutations and PTEN loss, mutant xenograft models and triple negative breast cancer xenograft models. Combined treatment with capivasertib and fulvestrant demonstrated a greater anti-tumour response in a range of human breast cancer PDX models representative of different breast cancer subsets. This included models without detectable mutations or alterations in PIK3CA, PTEN or AKT, as well as models with mutations or alterations in PIK3CA, PTEN or AKT.

Biomarker definition / definition of biomarker positivity:

Patients that fulfilled the eligibility criteria and consented to join the CAPItello-291 study were randomised irrespective of their 'tumour PIK3CA/AKT1/PTEN alteration status'. However, mandatory baseline tissue samples (newly collected or archival formalin-fixed, paraffin-embedded tissue block or tumour slides from the most recently collected tumour tissue sample, derived from the primary or recurrent cancer site) were required from all patients at screening and were analysed retrospectively, post randomisation, to assess the PIK3CA/AKT1/PTEN alteration status.

As to the following definition patients were assigned to the PIK3CA/AKT1/PTEN-altered analysis population:
'*Patients with breast cancer tumours harbouring at least one alteration in the PIK3CA, AKT1 or PTEN genes as detected by the FoundationOne®CDx (F1CDx) test and classified as per the CAPItello-291 biomarker rules (see table on 'Biomarker Rules for CAPItello-291' below)*'.

Table 54 Biomarker rules for CAPItello-291

Gene (Transcript)	Variant Class	Biomarker Rules
PIK3CA (NM_006218)	Short Variant [a]	C420R, E542K, E545A, E545D, E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations
PIK3CA (NM_006218)	Short Variant (AZ defined)	R88Q, N345K, E545Q, Q546K, Q546P, M1043V, M1043I, and G1049R
AKT1 (NM_001014431)	Short Variant (AZ defined)	Any short variant with protein effect E17K
PTEN (NM_000314)	Short Variant (AZ defined)	Any short variants listed below: C124R, C124S, G129E, G129V, G129R, R130Q, R130G, R130L, R130P, C136R, C136Y, S170R and R173C

		Any nonsense (including stop codons), frameshift, or splice site alteration, including those that affect the start codon (i.e. M1?, M1T, M1fs*23).
	Copy Number Alteration (AZ defined)	Any homozygous deletion of one or more exons, regardless of transcript
	Rearrangement [b] (AZ defined)	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.

[a] Variants previously FDA-approved per P170019/S006. AZ defined variants are not currently FDA approved

[b] *PTEN* Rearrangement not included in OncoScreen Plus™ biomarker rules

Source: Appendix 16.1.13 ‚PIK3CA/AKT1/PTEN Diagnostic Testing'(table 1, page 8/28)

Overall, the CAPItello-291 biomarker rules included:

- 19 PI3KCA short variants:
  - 11 short variants previously (FDA approved for alpelisib in the treatment of breast cancer)
  - 8 additional short variants (sponsor-defined)
- any AKT1 short variant with protein effect E17K (sponsor-defined)
- 13 PTEN short variants (sponsor-defined)
- PTEN copy number alteration and rearrangements (sponsor-defined).

As an exception for patients enrolled into study CAPItello-291 from mainland China the 'Burning Rock OncoScreen Plus™'' test was used instead of the F1CDx test. The biomarker rules employed were the same, with the exception that 'PTEN intragenic rearrangement' was not included due to limited analytical validation of OncoScreen Plus™ for these intragenic rearrangements. 8 Patients with valid 'OncoScreen Plus™' results were enrolled in study CAPItello-291, two of these 8 patients were tested biomarker-positive as defined above (both patients had PIK3CA alteration variant E545K).

During the evaluation it was clarified by the applicant that study specific documents on biomarker definitions and the type of test to be used were not yet in place during the first 7 months of enrolment. The relevant documents on biomarker definitions used during the study was provided by the applicant during the procedure. In Capitello-291 the first patient was enrolled on 16/04/2020, and the last patient was randomised on 13/10/2021. Tissue testing was performed between 22 August 2020 and 28 October 2021, apparently partly retrospective, partly real time. DCO was in August 2022.

The applicant clarified that biomarker rules defining biomarker positive status and used for F1CDx testing on CAPItello-291 were finalised with FMI on 30 November 2020 prior to the first data transfer on 21 December 2020 and that they did not change throughout the rest of the study.

The applicant clarified that the same biomarker definition was used for NGS-identified subgroup in FAKTION as in the CAPitello-291 study. In FAKTION, tissue for NGS analysis was available only for a subset of patients due to the retrospective approach for the updated analyses. With the intent to include the information for more patients, NGS analysis for detection of ctDNA in plasma was performed (Guardant Health OMNI). Apart from PTEN homozygous deletions which could not be detected in plasma (found in 2.4% of patients in CAPitello-291), the same biomarker definition was used as in CAPitello-291. Following this approach, NGS results became available for 80% (n=112) of the FAKTION-population.

Justification / validation of biomarker definition

As to the information applied, the justification for the definition of biomarker-positivity (i.e. PIK3CA/AKT1/PTEN alterations as specified above) is following a scientific rationale being mainly based on preclinical data. Regarding clinical validation see below.

Tests used

FoundationOne®CDx (F1CDx) (Foundation Medicine Inc., Cambridge, Massachusetts, USA), a tissue-based test, was used to determine the PIK3CA/AKT1/PTEN alteration status in the single pivotal study CAPItello-291. As an exception for patients enrolled into study CAPItello-291 from mainland China the 'Burning Rock OncoScreen Plus™' test was used instead of the F1CDx test. No local tests investigating the PIK3CA/AKT1/PTEN alteration status were performed.

Analytical method including assay platform, specimen, pre-analytical processing requirements and read-out method

F1CDx is an NGS-based in vitro diagnostic device for the detection of substitutions, insertion and deletion alterations (indels) and copy number alterations in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), homologous recombination deficiency, and tumour mutational burden (TMB) using DNA isolated from FFPE tumour tissue specimens.

F1CDx is a single-site assay performed at Foundation Medicine, Inc. in Cambridge, Massachusetts, USA. The assay includes reagents, software, instruments and procedures for testing DNA extracted from FFPE tumour tissue samples.

The assay employs a single DNA extraction method from routine FFPE tumour biopsy or surgical resection specimens, 50-1000 ng of which undergoes whole-genome shotgun library construction and hybridisation-based capture of a total of 324 genes (mostly targeting exons, for some genes also promotor regions, select intronic regions or noncoding RNAs). Using the Illumina® HiSeq 4000 platform, hybrid-capture–selected libraries will be sequenced to high uniform depth (targeting > 500x median coverage with >99% of exons at coverage >100x). Sequence data is processed using a customised analysis pipeline designed to detect all classes of genomic alterations, including base substitutions, indels, copy number alterations (amplifications and homozygous deletions), and selected genomic rearrangements (e.g. gene fusions).

Analytical validation strategy

Analytical validation of FoundationOne®CDx (F1CDx) with regard to accuracy, sensitivity, specificity, precision and robustness was demonstrated.

Clinical validation strategy

Treatment with capivasertib + fulvestrant resulted in an improvement in investigator-assessed PFS by RECIST 1.1 compared with placebo + fulvestrant in the Altered (i.e. biomarker-positive) Population (hazard ratio: 0.50; 95% CI: 0.38, 0.65).

A by-gene analysis of PFS for AKT1, PIK3CA and/or PTEN alteration status demonstrated efficacy that was consistent with the PIK3CA/AKT1/PTEN altered subpopulation in study CAPItello-291:

- AKT1 only (hazard ratio: 0.51, 95% CI: 0.22, 1.12)
- PIK3CA only (hazard ratio: 0.51, 95% CI: 0.37, 0.70)
- PTEN only (hazard ratio: 0.43; 95% CI, 0.21, 0.88)
- AKT1 independent (i.e., irrespective of the presence) of PIK3CA/PTEN (hazard ratio: 0.55, 95% CI: 0.26, 1.17)
- PIK3CA independent of AKT1/PTEN (hazard ratio: 0.51, 95% CI: 0.37, 0.69)
- PTEN independent of AKT1/PIK3CA (hazard ratio: 0.45, 95% CI: 0.24, 0.84)
- PIK3CA and/or AKT1 independent of PTEN (hazard ratio: 0.50, 95% CI: 0.38, 0.66)

- PIK3CA and/or AKT1 without (i.e., in the absence of) PTEN (hazard ratio: 0.50, 95% CI: 0.38, 0.67).

Table 55 Prevalence of individual PIK3CA/AKT1/PTEN gene alterations in CAPItello-291

Variant	Patients with valid result (N = 602), n (%)
***PIK3CA* alterations (included in FDA approved F1CDx)**	**205 (34.1%)**
C420R	6 (1.0%)
E542K	36 (6.0%)
E545A	3 (0.5%)
E545G	2 (0.3%)
E545K	56 (9.3%)
Q546E	1 (0.2%)
Q546R	1 (0.2%)
H1047Y	1 (0.2%)
H1047R	89 (14.8%)
H1047L	14 (2.3%)
***PIK3CA* alterations (sponsor-defined)**	**18 (3.0%)**
N345K	6 (1.0%)
E545Q	1 (0.2%)
Q546P	3 (0.5%)
Q546K	2 (0.3%)
R88Q	2 (0.3%)
G1049R	4 (0.7%)
AKT1 alterations short variant: missense E17K (sponsor-defined)	**37 (6.1%)**
***PTEN* short variants: missense (sponsor-defined)**	**3 (0.5%)**
R130Q	1 (0.2%)
R130G	1 (0.2%)
R130P	1 (0.2%)
PTEN short variants: protein truncating (sponsor-defined)	**31 (5.1%)**
Frameshift	20 (3.3%)
Nonsense	9 (1.5%)
Splice site	3 (0.5%)
PTEN large structural variants leading to loss (sponsor-defined)	**16 (2.7%)**
Rearrangement	2 (0.3%)
Copy number alterations	14 (2.3%)

Source: Appendix 16.1.13 ‚PIK3CA/AKT1/PTEN Diagnostic Testing'(table 8, page 17/28)

Cut-point selection

No information on cut-point selection (i.e. the threshold (i.e. cut-point) defining a patient as biomarker positive) was provided. The applicant clarified that unlike tests that measure protein expression levels (e.g. IHC), molecular tests are typically binary, based on limit of detection/limit of blank, determined as part of the analytical validation for performance characteristics. The detection and reporting of variants by the FMI analysis pipeline are not determined by a singular threshold, but rather, a number of thresholds and quality metrics that are set by the variant class (i.e. short variants, rearrangements, copy number amplifications and losses).

Discussion of other possible cut point definitions that could have an impact on the benefit-risk ratio of capivasertib was requested during the evaluation. Cut-points used for the respective genetic alteration defining "PIK3CA/AKT1/PTEN alteration-positivity" were provided for the central confirmation test 'F1CDx'. However, no clinical thresholding was performed. Albeit not ideal the applicant's clarifications are noted and this issue is considered as closed.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.5.6. Supportive study

FAKTION -A Phase Ib/II Randomised Placebo-controlled Trial of Fulvestrant +/- Capivasertib in Post-menopausal Women with Advanced Breast Cancer Previously Treated with a Third Generation Aromatase Inhibitor (Jones, Casbard et al. 2020)

As no CSR was submitted for the FAKTION study, this below section is based on the primary analysis published by Jones et al. 2020 (DCO: 30 January 2019) as well as discussions provided by the applicant in the dossier. Of note in July 2022 Howell et al. (Howell, Casbard et al. 2022) published an update of results on OS, PFS and expanded biomarker analyses (DCO: 25 November 2021) which are also discussed below.

Methods

The FAKTION study is a Phase Ib/II study funded by the applicant and Cancer Research UK as co-founder. According to the publication by Jones et al 2020 (Jones, Casbard et al. 2020), the applicant provided study medicinal products, contributed to study design and reviewed the draft analysis plan and the draft report.

- **Study participants**

Postmenopausal women with ER+ HER2- locally advanced or metastatic breast cancer, which had relapsed or progressed on an aromatase inhibitor with an ECOG status 0-2 were included.

- **Treatments**

Enrolled patients were to receive intramuscular fulvestrant 500 mg (day 1) every 28 days (plus a loading dose on day 15 of cycle 1) with either capivasertib 400 mg or matching placebo, orally twice daily on an intermittent weekly schedule of 4 days on and 3 days off (starting on cycle 1 day 15) until disease progression, unacceptable toxicity.

- **Objectives**

The primary objective for the Phase 2 part was to assess the relative anti-tumour activity of capivasertib + fulvestrant vs placebo + fulvestrant in terms of PFS in women with ER+ advanced breast cancer.

- **Outcomes/endpoints**

PFS was defined as the time from randomisation to either the first documented progression confirmed by RECIST criteria (regardless of whether the patient withdrew from study therapy or received another anti-cancer therapy before progression or death from any cause) assessed by the investigator.

Secondary endpoints included overall survival and ORR.

Analysis of the effect of PI3K pathway alteration on these outcomes was planned prospectively and subgroup analyses of progression-free survival, overall survival, and objective response by PI3K pathway alteration were additional secondary outcomes.

- **Randomisation and blinding (masking)**

Treatment allocation was done using an interactive web-response system using a minimisation method (with a 20% random element) and the following minimisation factors: measurable or non-measurable disease, primary or secondary aromatase inhibitor resistance, PIK3CA status, and PTEN status.

Blood and tissue samples were centrally tested for PIK3CA and PTEN alteration status before randomisation. Pathway alteration was protocol defined as either a hotspot mutation detected by digital droplet PCR (ddPCR) on PIK3CA exons 9 or 20 in tumour tissue or blood or an immunohistochemistry null status for PTEN in tumour tissue (primary tumour or metastatic biopsy). The method of mutational analysis changed from pyrosequencing to ddPCR during the trial (from 9 November 2016), which provided greater sensitivity to detect mutations. For 14 patients who were categorised as non-altered on the basis of initial pyrosequencing analysis had insufficient material to carry out a repeat ddPCR analysis.

Results

- **Baseline data**

Between 16 March 2015 and 06 March 2018, 183 patients were screened and 140 randomly assigned to receive capivasertib + fulvestrant (n = 69) or placebo + fulvestrant (n = 71).

Table 56 Baseline characteristics - Supportive FAKTION study (ITT population)

	Capivasertib + fulvestrant (n = 69)	**Placebo + fulvestrant (n = 71)**
Median age, years (IQR); range	62 (55, 68); 42, 81	61 (53, 68); 40, 82
ECOG PS, n (%)		
0	42 (61%)	49 (69%)
1	25 (36%)	17 (24%)
2	1 (1%)	2 (3%)
Missing	1 (1%)	3 (4%)
Stage, n (%)		
III inoperable	0 (0%)	1 (1%)
IV	68 (99%)	68 (96%)
Missing	1 (1%)	2 (3%)
Visceral disease, n (%)	49 (71%)	47 (66%)
Liver metastases, n (%)	32 (46%)	29 (41%)
Bone only disease, n (%)	10 (14%)	8 (11%)
Measurable disease, n (%)	49 (71%)	50 (70%)
Primary or secondary aromatase inhibitor resistance, n (%)		
Primary	25 (36%)	26 (37%)
Secondary	44 (64%)	45 (63%)

	Capivasertib + fulvestrant (n = 69)	Placebo + fulvestrant (n = 71)
Aromatase inhibitor given as last treatment before registration, n (%)	57 (83%)	52 (73%)
Previous adjuvant endocrine therapy, n (%)	60 (87%)	65 (92%)
Any tamoxifen	41 (68%)	43 (66%)
Any aromatase inhibitor	40 (67%)	36 (55%)
Any gonadotropin-releasing hormone	2 (3%)	1 (2%)
Other	1 (2%)	1 (2%)
Missing	0	1 (2%)
Previous endocrine treatment (metastatic or locally advanced setting), n (%)		
Median lines, (IQR); range	1 (1, 2); 0, 3	1 (1, 2); 0, 3
0 lines	9 (13%)	6 (8%)
1 line	39 (57%)	45 (63%)
≥ 2 lines	20 (29%)	20 (28%)
Missing	1 (1%)	0
Previous adjuvant chemotherapy, n (%)	36 (52%)	42 (59%)
Metastatic chemotherapy for advanced breast cancer, n (%)	17 (25%)	20 (28%)
Previous CDK 4/6 inhibitor, n (%)	0	0
PIK3CA results –blood or tissue, n (%)		
Wild type	42 (61%)	47 (66%)
Mutation	27 (39%)	24 (34%)
Missing	0	0
PTEN results, n (%)		
0	4 (6%)	4 (6%)
1	9 (13%)	8 (11%)
2	13 (19%)	23 (32%)
3	34 (49%)	28 (39%)
Missing	9 (13%)	8 (11%)

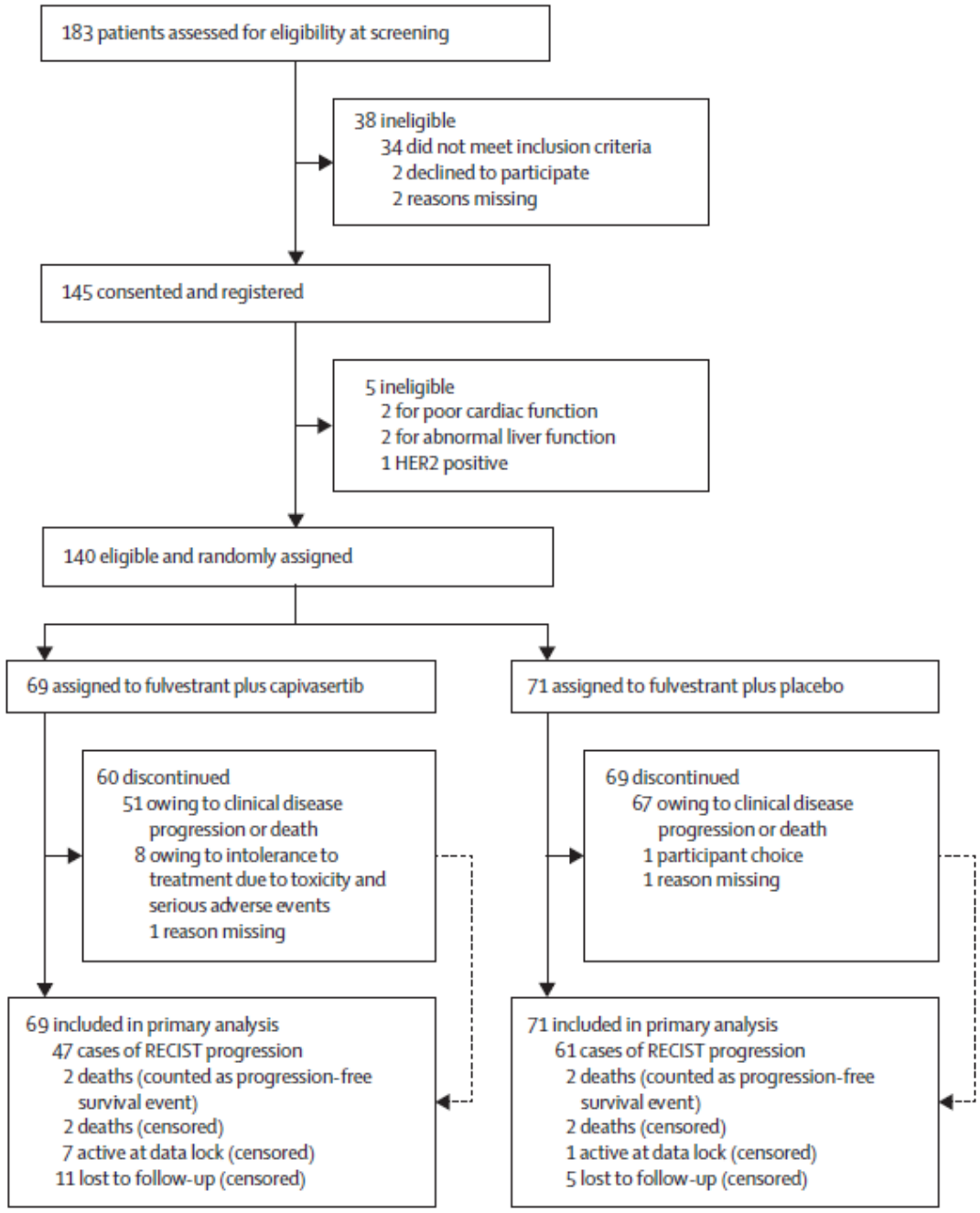
Adapted from Jones et al 2020

The analysis sets and the number of patients in each analysis set are summarised in the below table.

Table 57 Analysis populations 2020– Supportive FAKTION study

Population	Capivasertib + fulvestrant (n)	Placebo + fulvestrant (n)
ITT	69	71
PI3K/PTEN Pathway Altered	31	28
PI3K/PTEN Pathway Non-altered	38	43

Figure 24 Participant flow



From Jones et al 2020

In total, 183 patients were screened for eligibility, of whom 140 (77%) were eligible. A total of 69 and 71 patients were randomised to the capivasertib + fulvestrant and placebo + fulvestrant arms, respectively. Treatment groups were well balanced for baseline characteristics.

- **Outcomes and estimation**

Overall, in the ITT analysis by Jones et al 2020, PFS was significantly longer in patients who received capivasertib + fulvestrant than in those who received placebo + fulvestrant.

Table 58 FAKTION analyses 2020: Progression-free survival and overall survival

	ITT Population		PI3K/PTEN Pathway Altered Subgroup		PI3K/PTEN Pathway Non-altered Subgroup	
	C + F (N = 69)	P + F (N = 71)	C + F (N = 31)	P + F (N = 28)	C + F (N = 38)	P + F (N = 43)
Progression-free survival						
Number of events (%)	49 (71)	63 (89)	NR	NR	NR	NR
Median (months)	10.3	4.8	9.5	5.2	10.3	4.8
Adjusted HR (95% CI)	0.58 (0.39, 0.85)		0.59 (0.34, 1.03)		0.56 (0.33, 0.96)	
2-sided p-value	0.0049		0.064		0.035	
Overall survival						
Number of events (%)	21 (30)	31 (44)	NR	NR	NR	NR
Median (months)	26.0	20.0	30.5	18.7	23.7	20.3
Adjusted HR (95% CI)	0.59 (0.34, 1.05)		0.53 (0.21, 1.33)		0.62 (0.30, 1.28)	
2-sided p-value	0.071		0.17		0.20	

C, capivasertib; F, fulvestrant; P, placebo.

Source: Jones et al 2020

OS data reported by Jones et al. were immature with a median follow-up for survival of 12 months.

A recent publication by Howell et al 2022 - reported updated PFS and OS analyses from FAKTION and moreover expanded biomarker analyses.

For OS, mature results were reported for the ITT population with median OS of 29.3 months (95% CI 23.7–39.0) versus 23.4 months (18.7–32.7; adjusted HR 0.66 [95% CI 0.45–0.97]; two-sided p=0.035).

Updated PFS results for the ITT population were reported with median PFS of 10.3 months (95% CI 5.0-13.4) versus 4.8 months (3.1-7.9; adjusted HR 0.56 [95% CI 0.38–0.81]; two-sided p=0.023).

For expanded biomarker analyses, tissue and blood samples were re-analysed retrospectively in 2 steps. In the first step AKT mutation was included, in the second step of -expanded biomarker analyses NGS methods were included: FoundationOne for tissue (similar to CAPITELLO-291) and GuardantOMNI RUO for cfDNA. NGS results became available for 80% (n=112) of the FAKTION-population. Apart from PTEN homozygous deletions which could not be detected in plasma (found in 2.4% of patients in CAPitello-291), the same biomarker definition was used as in CAPitello-291.

This led to newly defined pathway altered and non-altered subgroups. The publication included a table with results for PFS and OS for the pathway altered and non-altered subgroups as originally identified, according to an expanded definition and a definition in which only NGS results are the basis for determination of the biomarker (see below).

Table 59 Progression free survival and overall survival in the intention to treat population and the PI3K/AKT/PTEN pathway-altered and pathway non-altered subgroups identified by original, expanded, and NGS testing

	Fulvestrant plus capivasertib group		Fulvestrant plus placebo group		Unadjusted HR (95% CI); two-sided p value	Adjusted HR (95% CI); two-sided p value
	Number of events/ number of patients (%)	Median (95% CI), months	Number of events/ number of patients (%)	Median (95% CI), months		
Progression-free survival in intention-to-treat population, months	54/69 (78%)	10·3 (5·0–13·4)	64/71 (90%)	4·8 (3·1–7·9)	0·55 (0·38–0·80); p=0·0019	0·56 (0·38–0·81); p=0·0023
Overall survival in intention-to-treat population, months	49/69 (71%)	29·3 (23·7–39·0)	59/71 (83%)	23·4 (18·7–32·7)	0·66 (0·45–0·96); p=0·030	0·66 (0·45–0·97); p=0·035
Progression-free survival in pathway-altered subgroups						
Original pathway-altered subgroup	26/31 (83%)	10·5 (6·6–18·7)	28/28 (100%)	5·2 (3·1–8·4)	0·51 (0·30–0·89); p=0·018	0·47 (0·26–0·84); p=0·011
Expanded pathway-altered subgroup	30/39 (77%)	12·8 (6·6–18·8)	36/37 (97%)	4·6 (2·8–7·9)	0·46 (0·28–0·75); p=0·0021	0·44 (0·26–0·72); p=0·0014
NGS-identified pathway-altered subgroup	25/34 (74%)	13·4 (6·6–20·7)	29/29 (100%)	3·1 (2·8–7·7)	0·35 (0·20–0·63); p=0·0004	0·36 (0·20–0·65); p=0·0007
Progression-free survival in pathway non-altered subgroups						
Original pathway non-altered subgroup	28/38 (74%)	10·3 (3·2–13·5)	36/43 (84%)	4·8 (3·0–10·3)	0·59 (0·35–0·99); p=0·044	0·59 (0·35–0·98); p=0·042
Expanded pathway non-altered subgroup	24/30 (80%)	7·7 (3·1–13·2)	28/34 (82%)	4·9 (3·2–10·5)	0·72 (0·41–1·27); p=0·25	0·70 (0·40–1·25); p=0·23
NGS-identified pathway non-altered subgroup	18/22 (82%)	4·8 (1·3–10·3)	22/27 (81%)	5·2 (2·2–10·5)	0·95 (0·50–1·81); p=0·88	0·95 (0·49–1·82); p=0·87
Overall survival in pathway-altered subgroups						
Original pathway-altered subgroup	20/31 (64%)	33·5 (22·3–50·7)	24/28 (86%)	20·9 (15·5–36·1)	0·51 (0·28–0·94); p=0·030	0·50 (0·27–0·92); p=0·025
Expanded pathway-altered subgroup	25/39 (64%)	38·9 (23·3–50·7)	32/37 (86%)	20·0 (14·8–31·4)	0·49 (0·29–0·84); p=0·0091	0·46 (0·27–0·79); p=0·0047
NGS-identified pathway-altered subgroup	21/34 (61%)	39·0 (22·3–50·7)	25/29 (86%)	20·9 (14·1–35·4)	0·43 (0·24–0·78); p=0·0056	0·44 (0·24–0·81); p=0·0076
Overall survival in pathway non-altered subgroups						
Original pathway non-altered subgroup	29/38 (76%)	26·2 (20·7–38·5)	35/43 (81%)	23·9 (16·3–33·3)	0·80 (0·47–1·30); p=0·37	0·80 (0·49–1·32); p=0·39
Expanded pathway non-altered subgroup	24/30 (80%)	26·0 (18·4–33·8)	27/34 (79%)	25·2 (20·3–36·2)	0·95 (0·55–1·64); p=0·85	0·86 (0·49–1·52); p=0·60
NGS-identified pathway non-altered subgroup	17/22 (77%)	23·7 (16·7–38·5)	22/27 (81%)	25·2 (15·3–38·8)	0·87 (0·46–1·64); p=0·66	0·86 (0·45–1·63); p=0·64

HR=hazard ratio. NGS=next-generation sequencing. NR=not reached.

By the NGS method two distinctly different populations with different treatment outcome were identified, while in the initial publication the treatment outcome was not influenced by biomarker status. The treatment effect in the non-altered subgroup which was reported by Jones et al. 2020 diminishes when the new definitions for biomarker positivity are used. For the non-altered subgroup, adjusted HR was 0.95 [95% CI 0.49, 1.82]. For the pathway altered population, adjusted HR was 0.35 [95% CI 0.20, 0.63]. The authors´ interpretation of the results is that in the original tests, patients with PIK3CA/AKT1/PTEN altered tumours were erroneously placed in the non-altered population and concluded that their analyses suggest "that NGS testing is needed to accurately identify patients who might not benefit from capivasertib" and the "expanded pathway non-altered subgroup analysis suggests, but does not prove, that capivasertib predominantly benefits patients with PIK3CA/AKT1/PTEN pathway alterations".

2.6.6. Discussion on clinical efficacy

As part of this MAA, the applicant submitted clinical study results in support of the following indication (wording amended during the evaluation):

> "*TRUQAP is indicated in combination with fulvestrant for the treatment of adult patients with oestrogen receptor (ER) positive, HER2 negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine-based regimen (see section 5.1*).
>
> *In pre- or perimenopausal women, TRUQAP plus fulvestrant should be combined with a luteinising hormone releasing hormone (LHRH) agonist.*

For men, administration of LHRH agonist according to current clinical practice standards should be considered."

The clinical development programme in support of the claimed indication consists of 2 clinical trials: one supportive phase 1b/2 study (FAKTION; performed in an academic context, funded by Cancer Research UK, with involvement of the applicant in funding, planning and reviewing) and the pivotal phase 3 study CAPItello-291.

Dose finding and dose recommendation

The recommended capivasertib dose is 800 mg daily (400 mg BD with or without food) for 4 days followed by 3 days off treatment, based on PK, PD, safety and efficacy data.

The recommended dosage of fulvestrant is 500 mg administered on Days 1, 15, and 29, and once monthly thereafter as approved in the EU. In pre/perimenopausal women, capivasertib plus fulvestrant should be combined with a luteinizing hormone releasing hormone (LHRH) agonist.

Because of the choice of dosage regimen for the fulvestrant combination, the usual approach to dose finding was not followed and the dosing regimen selection for the fulvestrant combination was mostly based on the selection of the dosing regimen for the capivasertib monotherapy.

As to the data provided, dose finding did not lead to an explicit recommended phase 2 dosing study. The decision to use the dosing regimen described above in the pivotal study CAPItello-291 was based on the FTIH study and consecutive clinical experience from the supportive phase 1b/2 FAKTION study. Although this dosing regimen is overall acceptable, based on the data provided it cannot be concluded whether the dosing regimen is optimal.

In terms of dose adjustment, a first dose reduction from 400 mg to 320 mg twice daily for 4 days followed by 3 days off treatment is proposed followed by a second dose reduction to 200 mg twice daily for 4 days followed by 3 days off treatment to manage adverse reactions. In order to further justify the proposed 2nd dose reduction scheme for Capivasertib rather than immediate discontinuation of treatment for all relevant populations, a post-hoc analysis was conducted to explore efficacy in patients with a dose reduction to capivasertib 200 mg in the pivotal CAPItello-291 study. These analyses showed no evidence of less benefit in patients with dose reductions to capivasertib 200 mg BD (versus placebo+fulvestrant and versus capivasertib+fulvestrant) hence supporting the proposed 2nd dose reduction.

Design and conduct of clinical studies

Pivotal study: CAPItello-291

The general design as a randomised, double-blind, placebo-controlled multicentre trial is endorsed. CHMP scientific advice (SA) on the design of the proposed pivotal phase 3 study (D3615C00001; CAPItello-291) was obtained in October 2019 (ref. EMEA/H/SA/3985/2/2019/III).

- **Inclusion and exclusion criteria**

The overall population includes several very relevant subgroups, e.g. pre/perimenopausal patients, postmenopausal patients, patients with prior CDK4/6i treatment, and CDK4/6I naïve patients, tumours with PIK3CA/AKT1/PTEN alteration, confirmed non-altered tumours and tumours for which biomarker test on PIK3CA/AKT1/PTEN was not successful.

In the CHMP scientific advice ,aspects of the inclusion and exclusion criteria were discussed, e.g. inclusion of pre- and post-menopausal patients, patients progressing after adjuvant therapy and on 1st line advanced therapy, respectively, and with or without previous chemotherapy exposure in the same study

was agreed for HR+/HER2- breast cancer patients. Furthermore, the impact of inclusion of CDK 4/6 inhibitors naïve patients on heterogeneity and the appropriateness of the comparator was addressed. CHMP highlighted the expectation of adequately interpretable data for all subgroups of interest.

The inclusion and exclusion criteria largely reflect the large and heterogeneous target population in endocrine (i.e. AI-) resistant advanced and metastatic breast cancer. It is agreed that patients with rapidly progressive disease are excluded in order to avoid complications of treatments that may induce tumour response in short time, e.g. chemo- or radiotherapy are preferred.

As CDK 4/6 inhibitors combined with endocrine treatment are recommended as first-line treatment in HR+/HER2- advanced breast cancer, it would have been expected that all patients previously treated in the metastatic setting would all have received CDK 4/6 inhibitors. The applicant's intention was to include both, CDK 4/6 inhibitors pre-treated (>50%) and CDK 4/6 inhibitors naïve patients. This increases the heterogeneity, which is already apparent, as pre/peri- and postmenopausal women and men with metastatic breast cancer (mBC) and patients with different lines of prior treatment are included in the single pivotal trial.

Inclusion of pre/peri- and postmenopausal women and men with mBC is acceptable in line with recent guidelines, provided that premenopausal women receive LHRH analogues for continuous ovarian suppression. The combination with LHRH analogues in pre- or perimenopausal women has been included in section 4.1 of the SmPC.

Patients with diabetes mellitus were excluded from the pivotal trial and additional data on the efficacy and also the safety in these patients are needed to give evidence-based recommendations to prescribers, when patients with concomitant diabetes mellitus should be part of the target population (see also section 2.6.8.). In the context of the capivasertib Phase IIIb programme (including studies CAPItana, CAPItrue and CAPIcorn) enrolment of patients with clinically stable diabetes mellitus (complying with eligibility criteria defined as HbA1c ≤8.0% (63.9 mmol/mol) at screening) should be encouraged and subgroup analyses on efficacy (ORR, PFS, OS) in diabetic patients in the individual studies and in the combined analyses should be planned. Results of such studies (CAPItana, CAPItrue and CAPIcorn) should be submitted once available (REC).

- **Biomarker PIK3CA/AKT1/PTEN alteration**

For investigation of PIK3CA/AKT1/PTEN alteration status a tumor sample – preferably FFPE or freshly-cut unstained serial tumor slides - was mandatory for central testing by FoundationOne®CDx (with the exception of 8 patients from mainland China due to restrictions in shipping tissue from China). For the definition of biomarker-positivity, several PIK3CA/AKT1/PTEN alterations were added to the PIK3CA alterations that were already FDA approved for the FoundationOne®CDx.

Clarification on the definitions of biomarker rules and timelines for implementation were requested during the evaluation. In Capitello-291 the first patient was enrolled on 16/04/2020 and the last patient on 13/10/2021. Tissue testing was performed between 22 August 2020 and 28 October 2021, apparently partly retrospective, partly in real time. DCO was in August 2022. The applicant clarified that biomarker rules defining biomarker positive status and used for F1CDx testing on CAPItello291 were finalised with FMI on 30 November 2020 prior to the first data transfer on 21 December 2020 and that they did not change throughout the rest of the study. In view of the role of the biomarker positive treatment group as primary analysis population, documentation in an appendix to the protocol prior to first patient first visit (FPFV) would have been expected.

CHMP scientific advice indicated that prospective NGS testing for PIK3CA/AKT1/PTEN alterations would have allowed stratification by PIK3CA/AKT1/PTEN alteration status. However, prospective NGS testing for PIK3CA mutations was not considered feasible by the applicant due to the delay of start of treatment

by ≥30 days. While this argument was accepted, CHMP highlighted the importance of the ability to assess consistency between the mutated and the non-mutated subgroups.

Furthermore, CHMP scientific advice requested subgroup analyses with regard to PI3K/AKT/PTEN pathway activation status (with the need to demonstrate and confirm the benefit regardless of biomarker status), and prior exposure to CDK 4/6 inhibitors (with the need to show the benefit in CDK 4/6 inhibitors pre-treated patients even in relation with biomarker status) was considered particularly relevant.

Next to the *overall population*, the *PI3K/AKT/PTEN altered population* is a primary population. For the *non-altered population* exploratory analyses were presented. For the benefit-risk, separate discussions for the PI3K/AKT/PTEN altered and for the *non-altered population*/*known non-altered population* were deemed necessary.

- **Randomisation**

The stratification factors: presence of liver metastases, prior use of CDK4/6 inhibitors and geographic location are endorsed. PI3K/AKT/PTEN alteration status would have been highly welcomed also as a stratification factor in view of the importance of the PI3K/AKT/PTEN altered population as a primary population.

- **Comparator placebo + fulvestrant**

Placebo + fulvestrant was chosen as comparator. Fulvestrant is included in current treatment guidelines for patients with no risk of organ failure. However, based on a substantial PFS benefit over endocrine monotherapy, CDK4/6I are recommended in combination with an AI or fulvestrant for first-line or second line endocrine treatment, respectively. Therefore, fulvestrant monotherapy is not considered as the best available treatment option in CDK 4/6 inhibitors naïve patients. This shortcoming was addressed as part of the CHMP Scientific advice. CHMP requested contextualisation of the results and a discussion on their clinical relevance in light of the best available alternative treatment options was expected to support the B/R assessment. In principal allowing fulvestrant + CDK4/6I to CDK4/6I naïve patients would have been a valuable option for the reference treatment arm, still allowing to assess the contribution of capivasertib in the doublet regimen under study, given that a large majority of the patients was intended to be pre-treated with CDK4/6I.

- **Endpoints**

Dual primary endpoints were planned for the study, PFS (by investigator assessment) in the *overall population* and the *PIK3CA/AKT1/PTEN altered population*. PFS assessment by investigator is considered appropriate in view of the blinded placebo-controlled design. It is acknowledged that sensitivity analyses for PFS include full BICR assessment which is considered important as blinding might have been compromised by capivasertib-associated adverse drug reactions.

Overall survival is a key secondary endpoint and analysed for both primary populations.

Overall response rate (best overall response rate), duration of response and PFS2 are relevant secondary endpoints, which are endorsed. All these clinical endpoints are planned for the *overall population* and the *PIK3CA/AKT1/PTEN altered population*. For the *non-altered population* exploratory analyses were planned for the same endpoints.

A number of further exploratory endpoints address different aspects of the biomarker role, including comparisons of PIK3CA/AKT1/PTEN alterations in ctDNA and tissue samples and comparisons of samples taken pre-treatment and on-treatment.

Standard safety endpoints to assess the safety and tolerability are endorsed. Patient reported outcomes include EORTC-QLQ-C30 and EORTC-BR23, PRO-CTCAE, and EQ-5D-5L health state utility index. These are standardised measures appropriate for the target population.

In the target population of patients with locally advanced or metastatic HR positive, HER2 negative breast cancer, PFS is the appropriate time-to-event endpoint for evaluation of the direct treatment effect. It is acceptable for the pivotal study provided the effect is homogeneous across important subpopulations, and PFS is sufficiently large to outweigh added toxicity, and that mature OS data at least exclude any detriment. The plan for two primary populations is agreed to allow a separate evaluation in the *PIK3CA/AKT1/PTEN altered population* next to the *overall population*. The complementary *non-altered population* is important for the assessment of homogeneity of subgroups.

- **Statistical methods**

The analyses were generally pre-specified in SAP 4.0 that was finalised before the primary PFS analysis database lock, however, the multiplicity procedure was changed to include spending small alpha for the first OS analysis after unblinding which was not ideal but not considered critical as the change did not result in confirmatory claims.

The FAS excludes patients randomised in China after the global cohort last patient first visit (LPFV), as pre-specified in the protocol. Analyses based on Chinese patients randomised before and after are described in a separate 'China SAP', reported in a separate CSR and are exploratory according to study protocol. No results from this cohort are provided in this application.

The primary PFS analysis was based on investigator's assessment, while an analysis using BICR was provided as sensitivity analysis. This is appropriate for a blinded study.

While defining time to PFS regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy prior to progression (i.e. patients were not censored in case of these events) is in accordance with the relevant EMA guidance on PFS, censoring patients in case of progression or death immediately after two consecutively missed visits is not. It is acknowledged that a sensitivity analysis reverting these two censoring rules was provided.

Standard methods for time to event analysis (log-rank test and Cox regression) were applied for hypothesis testing and treatment effect estimation for PFS and OS. The randomisation stratification factors were appropriately taken into account by a correspondingly stratified analysis.

In accordance with the pre-specified multiplicity procedure, confirmatory hypotheses tests were possible for PFS and OS in the *overall population* and the *PIK3CA/AKT1/PTEN altered population*, respectively. The multiple testing strategy was appropriate to ensure control of the family-wise type 1 error rate. The multiplicity strategy including alpha splitting would have allowed confirmatory conclusions for PFS for the overall and the altered population even if the null hypothesis for the *overall population* could not have been rejected and vice versa; consequently, considering the PFS analyses in these populations as dual primary was appropriate. The originally planned interim analysis for the *overall population* was removed in a protocol amendment (CSP V4.0) while the study was blinded, which is appreciated.

Although the testing strategy allows confirmatory conclusions for the *overall population* and the *altered population*, a positive result in the *overall population* could be driven by an effect in the *altered population* such that the exploratory analysis in the *Non-altered population* (including the *Known non-altered population* and the No Result Population) is particularly relevant.

No confirmatory conclusions can be drawn for OS. The nominal 95% confidence interval for the HR that was provided for OS is not consistent with the confirmatory testing strategy. In particular, an effect on OS based on the 95% CI excluding 1 cannot be claimed.

During the study conduct, 3 amendments were issued, the most fundamental ones concern the definition of the primary endpoint as dual primary endpoints in the overall and the *PIK3CA/AKT1/PTEN altered population* and the separation of the Chinese patients from the Global cohort. In June 2021, when the majority of patients was enrolled, the inclusion criteria were amended so that progression or recurrence on the most recent treatment was required.

A total of 62 patients were known for at least one important deviation (8.8%; 62/708). One of the most frequent protocol deviation (25%; 16/62) was patients receiving capivasertib/placebo at incorrect dose, mostly reduced dose for a given period of time. This could have possibly impacted the observed safety results by minimizing them. It seems that the wording of the posology may have lead to posology mistakes. The proposed SmPC section 4.2 is considered clear and understandable regarding posology, which is reassuring.

The applicant stated that 8 audits at investigator sites were performed and provided the audits certificates.

Efficacy data and additional analyses

Baseline characteristics

In the overall population, the median age was 58 years (range from 26 to 90 including 30.7% of patients over 65 years of age). Most patients were female (99.0%) and White (57.5%) followed by Asian (26.7%) and Black (1.1%). While the proportion of men in the study program is very low, it is still considered possible to extrapolate results to men, based on the common biological and pharmacological rationale. Most patients had Eastern Cooperative Oncology Group (ECOG) performance status 0 and the majority of patients was in postmenopausal state (77.3%). All patients received prior endocrine-based therapy (100% AI-based treatment and 44.1% received tamoxifen). Prior treatment with CDK4/6 inhibitor was reported in 70.1% of patients. Chemotherapy for locally advanced (inoperable) or metastatic disease was reported in 18.2% of patients.

Patient demographics for those in the PIK3CA/AKT1/PTEN-altered population were generally representative of the overall study population with some differences between arms. There were less patients with a pre/perimenopausal status, less in the youngest and oldest age cohorts and more patients with lung and/or liver metastases in the capivasertib arm.

In the 'Known non-altered population' capivasertib treatment group, slightly more patients presented with locally advanced disease, in postmenopausal state and without CDK 4/6I pre-treatment and with diabetes. There is no indicator for a more unfavourable prognosis in this treatment group.

In terms of subgroups, the pre-/perimenopausal subgroup presented with somewhat more advanced disease, more liver metastases and had less likely PIK3CA/AKT1/PTEN alterations. The CDK 4/6 inhibitors naïve subgroup included more patients from Asia, more in postmenopausal status, more (neo)adjuvant chemotherapy and substantially more patients with no prior endocrine based therapy for locally advanced or metastatic breast cancer.

Only patients with ER+ disease as per ASCO recommendation were in fact included in the study, in line with the mode of action for fulvestrant. The initially proposed indication wording was therefore changed from "hormone receptor positive breast cancer" to "oestrogen receptor (ER) positive".

Dual primary endpoints PFS in the overall and PIK3CA/AKT1/PTEN altered populations

Based on approximately 77% of events both primary endpoints of PFS (by *investigator assessment*) in the *overall* and in the *PIK3CA/AKT1/PTEN altered* populations were met. In both primary populations the

effect on PFS is statistically significant and in its reported size clinically relevant with doubling of the median PFS time i.e. 3-4 months.

In the *PIK3CA/AKT1/PTEN altered population* (40.8 % of the *overall population*), a reduction in the risk of progression in favour of capivasertib + fulvestrant was observed with a HR 0.50 (95% CI: 0.38 – 0.65; p < 0.001). The median PFS was 7.3 months in the capivasertib + fulvestrant arm compared with 3.1 months in the placebo + fulvestrant arm.

The effect on PFS is considered robust regarding the results of several sensitivity analyses (on ascertainment bias, evaluation time bias and attrition bias) which are consistent with the results for the primary analyses for both primary populations. The effect in the overall population was primarily attributed to the results seen in the *PIK3CA/AKT1/PTEN altered population*.

PFS in the *non-altered population*

Importantly, for the understanding of the treatment effect in the biomarker PIK3CA/AKT1/PTEN negative population, exploratory PFS analyses were submitted for the *non-altered population* (59.2 % of *overall population*) and its subgroups - *known non-altered* subgroup (44.2% of *overall population*) and *no-result* subgroup (15.0 % of *overall population*).

Although for the entire *non-altered population* the absolute effect size was similar to that in the *overall* and the *PIK3CA/AKT1/PTEN altered populations* , this is mainly due to the effect in the no-result population (HR 0.52 (95% CI: 0.32, 0.83)). The effect in the documented biomarker negative, i.e. *known non-altered population* was very limited with PFS by investigator HR 0.79 (95% CI: 0.61, 1.02) and PFS by BICR HR 0.85, (95% CI 0.65, 1.12).

Overall survival is a key secondary endpoint for both primary populations. After approximately 16 months of follow-up, data are still immature. For both the *overall population* and the *PIK3CA/AKT1/PTEN altered population*, the analyses on OS at the time of the primary PFS analysis did not suggest a detrimental effect on survival of treatment with capivasertib + fulvestrant compared with placebo + fulvestrant.

Further interim and final OS analyses will be provided with more mature data (scheduled DCO March 2024 and May 2025). The applicant indicated the interim and final analyses on OS should be available approximately in Q3 2024 and Q4 2025, respectively. The applicant agreed to provide both OS analyses as soon as they become available (REC).

Results of **PFS2** events need to be interpreted with caution, as standardised uniform tumour assessments cannot be assumed. Results showing a numerical trend in favour of capivasertib+fulvestrant for the *overall population* and the *PIK3CA/AKT1/PTEN altered population* go in the same direction as the primary results, whereas for the *known non-altered population* no relevant difference was reported. It is considered reassuring that there is no sign of detriment with capivasertib+fulvestrant.

Exploratory analyses on objective response rates for both primary populations by INV and BICR showed higher ORR for capivasertib+fulvestrant than for placebo+fulvestrant in both primary populations. Duration of response – based on small numbers - appeared similar in both arms.

<u>Supportive study FAKTION</u>

Results of the phase 2 part of the FAKTION study which investigated the combination capivasertib+fulvestrant vs placebo+fulvestrant in 140 patients with endocrine resistant HR positive locally advanced and metastatic breast cancer were reported by Jones et al 2020 and updated PFS and OS analyses and further biomarker analyses were reported by Howell et al 2022.

The study is relevant because the design as a placebo-controlled RCT is widely comparable to CAPITELLO-291, the dose and dose regimen are the same and there was a wide overlap in terms of the study populations. Both studies CAPITELLO-291 and FAKTION included HR+ HER2- advanced breast cancer patients following progression on AI. In comparison to CAPITELLO-291, the population in FAKTION is slightly older and postmenopausal, more in metastatic stage, and more patients had not received previous CDK 4/6 inhibitors, previous endocrine treatment appears slightly different, patients had received more tamoxifen, and more chemotherapy.

In FAKTION, blood and tissue samples were centrally tested for PIK3CA and PTEN alteration status before randomisation. As methods for detection of the biomarker "pathway" alteration evolved, the second publication reported results for newly defined pathway altered and pathway non altered populations, based on NGS methods that are comparable to those used in CAPItello-291 (only PTEN homozygous deletions could not be detected in plasma).

While the original analyses – using ddPCR and IHC for a limited set of alterations - found no impact of the biomarker status on the PFS and OS results, the updated results – using NGS and a wider set of alterations – found two distinctly different populations with different treatment outcome. The treatment effect in the non-altered subgroup which was reported by Jones et al 2020 diminished when the new definitions for biomarker positivity are used: for the non-altered subgroup the adjusted HR is 0.95 [95% CI 0.49, 1.82]. For the pathway altered population, the adjusted HR is 0.35 [95% CI 0.20, 0.63] is reported. The authors' interpret indicated "that NGS testing is needed to accurately identify patients who might not benefit from capivasertib" and the "expanded pathway non-altered subgroup analysis suggests, but does not prove, that capivasertib predominantly benefits patients with PIK3CA/AKT1/PTEN pathway alterations".

CHMP scientific advice highlighted the heterogeneity of the broad target population and requested adequately interpretable data for all subgroups of interest and indicated the need to demonstrate and confirm the benefit regardless of biomarker status, and prior exposure to CDK 4/6 inhibitors.

PFS analyses by further important subgroups

CHMP scientific advice highlighted the heterogeneity of the target population and requested adequately interpretable data for all subgroups of interest, this included prior exposure to CDK 4/6 inhibitors.

- Efficacy by previous CDK4/6i treatment

A majority of patients (70.1%) had received a prior CDK4/6i. For the remaining 29.9%, the reference treatment with fulvestrant monotherapy is not in line with recent clinical guidelines (Gennari, André et al. 2021). It is apparent that the proportion of CDK 4/6 inhibitor naïve patients varies within region, with the highest proportion in region 3 (Asia) and the lowest in region 1 (including North America and Western Europe, 12%). The applicant provided details for not being treated with a CDK4/6I. The main reasons were Health Care Providers preference (37.3%), followed by treatment not approved (25.3%), treatment not reimbursed (18.1%). Thus, for the latter two, CDK4/6 treatment was objectively not available.

A similar relative benefit in PFS was observed independent of prior exposure to CDK4/6 inhibitors (HR of 0.59 and 0.64 respectively). A shorter absolute PFS in both treatment arms was associated with prior use of CDK4/6 inhibitors. Although small, the absolute size of median PFS in the placebo + fulvestrant arm in patients pre-treated with CDK 4/6 inhibitors (2.6 months) is in line with recent publications (Lindeman, Bowen et al. 2021, Bidard, Kaklamani et al. 2022) and therefore considered acceptable.

- Efficacy in premenopausal women

Pre/perimenopausal patients are an important subgroup of the target population for which conclusions on efficacy are considered important. It was clarified that nearly all pre-/perimenopausal women actually received LHRH analogues throughout the study. According to the baseline characteristics, pre-

/perimenopausal patients appeared to have somewhat more advanced disease, and had less likely PIK3CA/AKT1/PTEN alterations. In the subgroup of pre/perimenopausal women the effect size was smaller and the 95% CI crossed 1 (HR of 0.86, 95% CI 0.60-1.20). As the FAKTION study did not include pre-/perimenopausal women, there are no supportive data. The applicant indicated that further studies are investigating capivasertib in combination with other medicinal products (CAPItello-292 and CAPItello-290) and will provide further efficacy data for capivasertib in women in premenopausal state. The applicant agreed to provide results of CAPItello-292 and CAPItello-290 once available to address the efficacy in pre-menopausal women (REC).

It is reassuring that for patients with prior chemotherapy in the locally advanced/metastatic setting, an important subgroup with possibly poorer prognosis, results did not indicate impaired efficacy.

2.6.7. Conclusions on the clinical efficacy

The dual primary endpoint PFS (by investigator assessment) showed a statistically significant effect in favour of capivasertib + fulvestrant compared to placebo + fulvestrant both in the *overall population* and the *PIK3CA/AKT1/PTEN altered population*. In both primary populations, the size of the PFS effect is considered clinically relevant with doubling of the median PFS time i.e. 3-4 months.

In the entire *non-altered population* the absolute effect size was similar to that in the *overall population* and the *PIK3CA/AKT1/PTEN altered population* however this is mainly due to the PFS effect observed in the no-result part of the *non-altered population.* Therefore, the indication was restricted to patients with a PIK3CA/AKT1/PTEN tumour alteration.

Data for the key secondary endpoint OS are still immature after approximately 16 months of follow-up but for both the *overall population* and the *PIK3CA/AKT1/PTEN altered population*, the analyses on OS at the time of the primary PFS analysis did not suggest a detrimental effect on survival of treatment with capivasertib + fulvestrant compared with placebo + fulvestrant. Kaplan-Meier plots appearing to diverge early. Further interim and final OS analyses will be provided with more mature data (scheduled DCO March 2024 and May 2025).

In conclusion, the efficacy of capivasertib in combination with fulvestrant is considered established for the treatment of adult patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alterations following recurrence or progression on or after endocrine-based therapy.

2.6.8. Clinical safety

Table 60 Safety analysis sets

Analysis set	Number of patients	Definition	Purpose
CAPItello-291 SAS	Capivasertib + fulvestrant: N = 355 Placebo + fulvestrant: N = 350	All patients in the CAPItello-291 Overall Population who received at least 1 dose of study drug (fulvestrant, capivasertib, placebo), analysed according to the treatment received.	Provide the pivotal safety data to evaluate the safety and tolerability of capivasertib + fulvestrant in the intended patient population. The capivasertib + fulvestrant arm is the basis for identifying common ADRs and their frequency. The placebo control provides the basis for evaluating the contribution of capivasertib to the safety profile of the combination therapy with fulvestrant.

FTIH Study Pool	Capivasertib + fulvestrant: N = 75	All patients from the FTIH study (D3610C00001), Parts E and F, who received at least 1 dose of capivasertib.	Understand any differences in safety data between the CAPItello-291 SAS and the Combined Pool.
Combined Pool	Capivasertib + fulvestrant: N = 430	All patients in the capivasertib + fulvestrant arm of the CAPItello-291 SAS and all patients in the FTIH Study Pool.	Support evaluation and characterisation of common AEs.
Monotherapy Pool	Capivasertib: N = 165	All patients from the FTIH study (D3610C00001), Parts A to D, the Japanese safety/PK study (D3610C00004), and the formulation/food study (D3610C00007) who received at least 1 dose of capivasertib monotherapy at a dose of 480 mg BD 4 days on, 3 days off.	Indicate the potential contribution of capivasertib monotherapy to the safety profile when combined with fulvestrant.
FAKTION study	Capivasertib + fulvestrant: N = 69 Placebo + fulvestrant: N = 71	Phase II part	Supportive data

2.6.8.1. Patient exposure

CAPItello-291 study

As of the data cut-off (15 August 2022), median duration of follow-up was 14.9 months in the capivasertib + fulvestrant arm and 14.3 months in the placebo + fulvestrant arm.

Table 61 Duration of treatment (CAPItello-291 SAS- DCO: 15-08-2022)

		Capivasertib + Fulvestrant (N = 355)	Placebo + Fulvestrant (N = 350)
Total (intended) treatment duration (months) – capivasertib/placebo [a]	Median	5.42	3.58
	Range	0.1–26.3	0.1–25.0
	Total treatment years	211.0	164.2
Total (intended) treatment duration (months) – fulvestrant [b]	Median	5.75	3.68
	Range	0.5–26.3	0.5–25.1
	Total treatment years	233.5	172.0
Actual treatment duration (months) – capivasertib/placebo [c]	Median	5.29	3.52
	Range	0.1–26.0	0.1–23.6
	Total treatment years	206.7	162.2

[a] Total treatment duration = (date of last dose date where dose > 0 - first dose date + 1)/(365.25/12).

[b] Total treatment duration = (min (date of last dose where dose > 0 + D, date of death, date of DCO) – first dose date + 1)/(365.25/12), where D is equal to the scheduled number of days between doses minus one.

[c] Actual treatment duration = total treatment duration minus the total duration of dose interruptions. Total treatment years is calculated as total treatment duration in months summed over patients divided by 12.

The median relative dose intensities of capivasertib and placebo were 93.8% and 99.5%, respectively.

The median percentage of the actual dose delivered relative to the intended dose (relative dose intensity) was 95.3% (78.0%, 100.0%) for capivasertib, 99.7% (96.6%, 100.0%) for placebo, and 100% (100.0%, 100.0%) for fulvestrant in both treatment groups.

The exposures and relative dose intensities in the altered subgroup safety analysis set were similar to those of the overall safety population.

In the confirmed non-altered subgroup the median total and actual duration of exposure to capivasertib were shorter (3.6. and 3.2 months, respectively) than in the overall population, and were comparable to placebo + fulvestrant arm.

The safety data update included data for all patients who received the study drug in the Overall Population of CAPItello-291 with DCO 27 March 2023. The median total treatment duration remained the same, 5.4 months vs 3.6 months for capivasertib and placebo, respectively, and total treatment duration increased by 29.1 total treatment years for capivasertib (211.0 and 240.1 total treatment years at DCO1 and 27 March 2023 DCO, respectively) and by 21.9 total treatment years for placebo (164.2 and 186.1 total treatment years, respectively).

<u>FAKTION study</u>

As of the DCO of 30 January 2019, the median duration of capivasertib treatment (capivasertib + fulvestrant arm) was 7.7 (1.5 to 13.5) months. The median duration of fulvestrant treatment was 9.2 (3.0 to 14.1) months in the capivasertib + fulvestrant arm and 4.6 (2.8 to 10.5) months in the placebo + fulvestrant arm. The median duration of placebo treatment (placebo + fulvestrant arm) was 4.9 (2.3 to 10.6) months.

2.6.8.2. Adverse events

Table 62 Adverse events in any category – study CAPItello-291 (SAS and altered subgroup SAS) at DCO: 15 August 2022

Any AE	**Number (%) of patients [a]**			
	Overall population		**Altered subgroup**	
	Capivasertib + Fulvestrant (N = 355)	**Placebo + Fulvestrant (N = 350)**	**Capivasertib + Fulvestrant (N = 155)**	**Placebo + Fulvestrant (N = 133)**
	343 (96.6)	**288 (82.3)**	**151 (97.4)**	**112 (84.2)**
Any AE possibly related to capivasertib/placebo	318 (89.6)	166 (47.4)	139 (89.7)	67 (50.4)
Any AE possibly related to capivasertib/placebo only [b]	308 (86.8)	129 (36.9)	137 (88.4)	53 (39.8)
Any AE possibly related to both capivasertib/placebo and fulvestrant [b]	91 (25.6)	66 (18.9)	40 (25.8)	27 (20.3)
Any AE possibly related to fulvestrant only [b]	65 (18.3)	65 (18.6)	33 (21.3)	23 (17.3)
Any AE of CTCAE Grade 3 or higher	152 (42.8)	55 (15.7)	65 (41.9)	21 (15.8)
Any SAE with outcome of death	4 (1.1)	1 (0.3)	2 (1.3)	1 (0.8)
Any SAE (including events with outcome of death)	57 (16.1)	28 (8.0)	28 (18.1)	14 (10.5)
Any AE leading to discontinuation of capivasertib/placebo	46 (13.0)	8 (2.3)	16 (10.3)	3 (2.3)
Any AE leading to discontinuation of capivasertib/placebo only	33 (9.3)	2 (0.6)	10 (6.5)	1 (0.8)
Any AE leading to discontinuation of both capivasertib/placebo and fulvestrant	13 (3.7)	6 (1.7)	6 (3.9)	2 (1.5)
Any AE leading to discontinuation of fulvestrant only	1 (0.3)	0	0	0
Any AE leading to dose modification of capivasertib/placebo	156 (43.9)	43 (12.3)	70 (45.2)	18 (13.5)
Any AE leading to dose interruption of capivasertib/placebo [c]	138 (38.9)	43 (12.3)	60 (38.7)	18 (13.5)
Any AE leading to dose interruption of capivasertib/placebo only	124 (34.9)	36 (10.3)	55 (35.5)	14 (10.5)
Any AE leading to dose interruption of both capivasertib/placebo and fulvestrant	22 (6.2)	9 (2.6)	9 (5.8)	4 (3.0)
Any AE leading to dose interruption of fulvestrant only	6 (1.7)	2 (0.6)	3 (1.9)	0
Any AE leading to dose reduction of capivasertib/placebo only [c]	70 (19.7)	6 (1.7)	33 (21.3)	1 (0.8)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

[b] As assessed by the investigator.

[c] The number of dose modifications due to AEs in the exposure summary (capivasertib + fulvestrant arm: 73 patients with dose reductions due to AEs and 137 patients with interruptions due to AEs; placebo + fulvestrant arm: 6 patients with dose reductions due to AEs and 38 patients with interruptions due to AEs; see Section 12.1) differs from the number of AEs resulting in a dose modification in this table (capivasertib + fulvestrant arm: 70 patients with AE leading to dose reduction and 138 patients with AEs leading to interruption; placebo + fulvestrant arm: 6 patients with AEs leading to dose reduction and 43 patients with AEs leading to interruption) due to the differences in data capture between the exposure and AE eCRFs.

Adverse events with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing; AEs occurring up to 30 days (+ 7 days) following date of last dose are reported.

CTCAE version 5 (23 September 2018).

MedDRA version 25.0.

Common AEs

Table 63 CAPItello-291, FTIH study pool, and combined pool: most common AEs (Frequency > 5% in any treatment group) (SAS), DCO: 15 August 2022

MedDRA PT	Number (%) of patients [a]			
	CAPItello-291		FTIH Study Pool	Combined Pool
	Capivasertib + fulvestrant (N = 355)	Placebo + fulvestrant (N = 350)	Capivasertib + fulvestrant (N = 75)	Capivasertib + fulvestrant (N = 430)
Patients with any AE	343 (96.6)	288 (82.3)	74 (98.7)	417 (97.0)
Diarrhoea	257 (72.4)	70 (20.0)	49 (65.3)	306 (71.2)
Nausea	123 (34.6)	54 (15.4)	37 (49.3)	160 (37.2)
Rash [b]	78 (22.0)	15 (4.3)	7 (9.3)	85 (19.8)
Fatigue	74 (20.8)	45 (12.9)	17 (22.7)	91 (21.2)
Vomiting	73 (20.6)	17 (4.9)	20 (26.7)	93 (21.6)
Headache	60 (16.9)	43 (12.3)	13 (17.3)	73 (17.0)
Decreased appetite	59 (16.6)	22 (6.3)	18 (24.0)	77 (17.9)
Hyperglycaemia	58 (16.3)	13 (3.7)	14 (18.7)	72 (16.7)
Rash maculo-papular [b]	57 (16.1)	9 (2.6)	15 (20.0)	72 (16.7)
Stomatitis	52 (14.6)	17 (4.9)	11 (14.7)	63 (14.7)
Asthenia	47 (13.2)	36 (10.3)	7 (9.3)	54 (12.6)
Pruritus	44 (12.4)	23 (6.6)	10 (13.3)	54 (12.6)
Anaemia	37 (10.4)	17 (4.9)	10 (13.3)	47 (10.9)
Urinary tract infection	36 (10.1)	23 (6.6)	6 (8.0)	42 (9.8)
Arthralgia	33 (9.3)	38 (10.9)	8 (10.7)	41 (9.5)
Aspartate aminotransferase increased	33 (9.3)	34 (9.7)	10 (13.3)	43 (10.0)
Alanine aminotransferase increased	32 (9.0)	30 (8.6)	7 (9.3)	39 (9.1)
Back pain	32 (9.0)	24 (6.9)	12 (16.0)	44 (10.2)
Pyrexia	32 (9.0)	14 (4.0)	9 (12.0)	41 (9.5)
Constipation	28 (7.9)	29 (8.3)	8 (10.7)	36 (8.4)
Dry skin	25 (7.0)	15 (4.3)	5 (6.7)	30 (7.0)
Dyspnoea	25 (7.0)	23 (6.6)	4 (5.3)	29 (6.7)
Pain in extremity	23 (6.5)	23 (6.6)	3 (4.0)	26 (6.0)
COVID-19	22 (6.2)	11 (3.1)	0	22 (5.1)
Insomnia	22 (6.2)	21 (6.0)	4 (5.3)	26 (6.0)
Abdominal pain	21 (5.9)	10 (2.9)	12 (16.0)	33 (7.7)
Dysgeusia	21 (5.9)	4 (1.1)	3 (4.0)	24 (5.6)
Dry mouth	19 (5.4)	9 (2.6)	2 (2.7)	21 (4.9)
Dyspepsia	18 (5.1)	7 (2.0)	1 (1.3)	19 (4.4)

Hot flush	18 (5.1)	19 (5.4)	5 (6.7)	23 (5.3)
Hypertension	18 (5.1)	13 (3.7)	5 (6.7)	23 (5.3)
Cough	17 (4.8)	13 (3.7)	7 (9.3)	24 (5.6)
Blood creatinine increased	16 (4.5)	2 (0.6)	4 (5.3)	20 (4.7)
Dizziness	16 (4.5)	12 (3.4)	12 (16.0)	28 (6.5)
Myalgia	16 (4.5)	18 (5.1)	3 (4.0)	19 (4.4)
Abdominal pain upper	13 (3.7)	11 (3.1)	4 (5.3)	17 (4.0)
Blood alkaline phosphatase increased	13 (3.7)	12 (3.4)	6 (8.0)	19 (4.4)
Weight decreased	12 (3.4)	8 (2.3)	8 (10.7)	20 (4.7)
Neutrophil count decreased	9 (2.5)	8 (2.3)	6 (8.0)	15 (3.5)
Oedema peripheral	7 (2.0)	9 (2.6)	4 (5.3)	11 (2.6)
Erythema	6 (1.7)	2 (0.6)	4 (5.3)	10 (2.3)
Hypomagnesaemia	5 (1.4)	2 (0.6)	4 (5.3)	9 (2.1)
Peripheral sensory neuropathy	4 (1.1)	6 (1.7)	5 (6.7)	9 (2.1)
Upper respiratory tract infection	4 (1.1)	2 (0.6)	6 (8.0)	10 (2.3)
Electrocardiogram QT prolonged	3 (0.8)	0	4 (5.3)	7 (1.6)
Flatulence	1 (0.3)	3 (0.9)	4 (5.3)	5 (1.2)
Nasal congestion	1 (0.3)	0	6 (8.0)	7 (1.6)

[a] Number (%) of patients with AEs, sorted in descending frequency of PT in the capivasertib + fulvestrant arm of CAPItello-291. Patients with multiple AEs are counted once for each PT.

[b] These PTs are included in the AESI grouped term of rash.

MedDRA Version 25.0.

Monotherapy Pool

In the Monotherapy Pool, the most frequently reported AEs were diarrhoea (79.4%), nausea (52.7%), hyperglycaemia (43.6%), fatigue (41.2) and vomiting (40.6).

Grade 3 or higher AEs

Table 64 CAPItello-291, FTIH study pool, and combined pool: AEs of CTCAE grade 3 or higher (frequency > 2% in any treatment group) (SAS)

MedDRA PT	Number (%) of patients [a]			
	CAPItello-291		FTIH Study Pool	Combined Pool
	Capivasertib + fulvestrant (N = 355)	Placebo + fulvestrant (N = 350)	Capivasertib + fulvestrant (N = 75)	Capivasertib + fulvestrant (N = 430)
Patients with any CTCAE ≥ Grade 3 AE	152 (42.8)	55 (15.7)	40 (53.3)	192 (44.7)
Diarrhoea	33 (9.3)	1 (0.3)	4 (5.3)	37 (8.6)
Rash maculo-papular [b]	22 (6.2)	0	8 (10.7)	30 (7.0)
Rash [b]	19 (5.4)	1 (0.3)	0	19 (4.4)
Hyperglycaemia	8 (2.3)	1 (0.3)	4 (5.3)	12 (2.8)
Hypokalaemia	8 (2.3)	0	1 (1.3)	9 (2.1)
Alanine aminotransferase increased	7 (2.0)	3 (0.9)	3 (4.0)	10 (2.3)
Aspartate aminotransferase increased	7 (2.0)	7 (2.0)	3 (4.0)	10 (2.3)

Vomiting	6 (1.7)	2 (0.6)	2 (2.7)	8 (1.9)
Nausea	3 (0.8)	2 (0.6)	3 (4.0)	6 (1.4)
Dehydration	2 (0.6)	0	2 (2.7)	4 (0.9)
Back pain	1 (0.3)	3 (0.9)	3 (4.0)	4 (0.9)
Electrocardiogram QT prolonged	1 (0.3)	0	2 (2.7)	3 (0.7)
Hypercalcaemia	1 (0.3)	2 (0.6)	2 (2.7)	3 (0.7)
Hypertransaminasaemia	0	0	2 (2.7)	2 (0.5)

[a] Number (%) of patients with AEs of CTCAE Grade 3 or higher, sorted in descending frequency of PT in the capivasertib + fulvestrant arm of CAPItello-291. Patients with multiple AEs are counted once for each PT.

[b] These PTs are included in the AESI grouped term of rash.

CTCAE Version 4.0 was used in the FTIH study (D3610C00001) and Version 5.0 in CAPItello-291. MedDRA Version 25.0.

FAKTION STUDY

As of the DCO of 30 January 2019, AEs of CTCAE Grade 3 or higher were reported in 45 (65.2%) patients in the capivasertib + fulvestrant arm and 35 (49.3%) patients in the placebo + fulvestrant arm in FAKTION (Jones et al 2020). The most common AEs of CTCAE Grade 3 to 4 were hypertension (22 [32%] patients in the capivasertib + fulvestrant arm and 17 [24%] patients in the placebo + fulvestrant arm), rash (grouped term; note, the PTs in this grouped term were not specified and may or may not align with the rash grouped term in CAPItello-291 (14 [20%] and 0 patients, respectively), diarrhoea (10 [14%] and 3 [4%] patients, respectively), infection (including UTI) (4 [6%] and 2 [3%] patients, respectively), and fatigue (one [1%] and 3 [4%] patients, respectively).

Adverse events of special interest

The AESIs for capivasertib include hyperglycaemia, diarrhoea (termed non-infectious diarrhoea in the CSP), rash, QT prolongation, infective pneumonia, stomatitis and UTI.

Hyperglycaemia

Patients with type 2 diabetes were eligible for CAPItello-291 if HbA1C at screening was less than 8.0% (63.9 mmol/mol), and if they did not require insulin treatment. Patients with type 1 diabetes were not eligible.

At a population level, median fasted glucose in both treatment arms was within the normal range at baseline (capivasertib + fulvestrant arm, 5.39 mmol/L; placebo + fulvestrant arm, 5.33 mmol/L), and for the duration of the on-treatment period, except for Cycle 2 Week 3 Day 1 in the placebo + fulvestrant arm (6.68 mmol/L).

At baseline, 34 (9.6%) patients in the capivasertib + fulvestrant arm and 20 (5.7%) patients in the placebo + fulvestrant arm had diabetes mellitus. Of the patients who had a hyperglycaemia event, 10 patients in the capivasertib + fulvestrant arm and 4 patients in the placebo + fulvestrant arm had a history of diabetes mellitus.

The incidence of hyperglycaemia AESIs (which included the PTs hyperglycaemia and blood glucose increased) was higher in the capivasertib + fulvestrant arm (16.9% of patients vs 4.0% of patients in the placebo + fulvestrant arm).

In patients where hyperglycaemia was reported as an AE, the first event typically occurred within the initial few weeks of treatment. Most of these AEs were CTCAE Grade 1 or 2.

Hyperglycaemia AESIs of CTCAE Grade 3 were reported in 7 patients (2.0%) in the capivasertib + fulvestrant arm and 1 patient (0.3%) in the placebo + fulvestrant arm. A hyperglycaemia AESI of CTCAE Grade 4 was reported for 1 patient (0.3%) in the capivasertib + fulvestrant arm; this patient had an ongoing medical history of obesity. The patient developed grade 4 hyperglycaemia 5 days after the most recent dose of capivasertib, and presented with altered sensorium. The patient had an additional SAE of sepsis 2 days later with an outcome of death the following day (see also section SAEs and deaths).

Of those patients in the capivasertib + fulvestrant arm with hyperglycaemia AESIs that required treatment (28 of 60 patients), the most common anti-diabetic agent received was metformin but 10 patients required also insulin therapy. Few patients required capivasertib dose interruptions (9 patients) or reductions (2 patients), and only one AESI of hyperglycaemia led to discontinuation of capivasertib.

At the time of DCO1, the events were recovered or recovering in the 37 out of 60 patients experiencing hyperglycaemia, and had not recovered in 28 of the 60 patients.

Table 65 Other AEs related to hyperglycaemia (SAS)

	Number (%) of patients			
	Capivasertib + Fulvestrant (N = 355)			**Placebo + Fulvestrant (N = 350)**
	Total	**Grade 3**	**Grade 4**	**Total**
Glycosylated haemoglobin increased	5 (1.4)	0	0	0
Diabetes mellitus	1 (0.3)	0	0	0
Diabetic ketoacidosis	1 (0.3)	0	1 (0.3)	0
Diabetic metabolic decompensation	2 (0.6)	1 (0.3)	0	0

The AE of Grade 4 diabetic ketoacidosis was reported in a patient with pre-existing type 2 diabetes mellitus and baseline HbA1C of 7.6% and fasting blood glucose of 9.546 mmol/L. The patient had intercurrent UTI which may have contributed to this complication of the patient's diabetes. The diabetic ketoacidosis led to discontinuation of capivasertib.

There were 2 AEs of diabetic metabolic decompensation. One (CTCAE Grade 3) occurred in a patient who took capivasertib for 14 consecutive days prior to the event and who had concomitant SAEs of diarrhoea, described as intense diarrhoea with weight loss and signs and symptoms of dehydration, and renal failure. The other was Grade 2 and occurred in a patient concomitantly receiving 3 antidiabetic agents (dapaglifozin, pioglitazone, alogliptin). No action was taken with the study treatments and the patient recovered.

Diarrhoea

The incidence of diarrhoea AESIs was higher in the capivasertib + fulvestrant arm (72.4% vs 20.3% in placebo + fulvestrant arm). Patients experiencing diarrhoea had a median of 1 diarrhoea AESI, most events occurred during the first cycle of treatment, and were mostly CTCAE Grade 1. Few patients (2%) discontinued treatment with capivasertib due to AESIs of diarrhoea. Most events were managed with treatment such as loperamide. Capivasertib interruptions and reductions were reported in 35 and 28 patients, respectively.

In the capivasertib + fulvestrant arm, 33 patients (9.3%) had diarrhoea events of CTCAE Grade 3, and 6 (1.7%) patients had SAEs of diarrhoea.

The following AEs were reported with a close temporal relationship (during or within 7 days of a diarrhoea AE) in a small number of patients in the capivasertib + fulvestrant arm: dehydration (4 patients),

hyponatremia (3 patients), hypokalaemia (8 patients), creatinine increase (10 patients), and acute kidney injury (5 patients).

In general, diarrhoea events occurred early on, with few patients experiencing their first diarrhoea AESI after 4 months of treatment.

Rash

The incidence of rash AESIs was higher in the capivasertib + fulvestrant arm then in placebo+ fulvestrant arm (38.0% vs 7.1%, respectively), and occurred with greater severity (CTCAE Grade 3: 12.1% vs 0.3%, respectively). Patients experiencing rash had a median of 1 rash event, with most events starting already during the first cycle of treatment. Of those patients with rash AESIs that required treatment (109 of 135 patients), most were managed with topical corticosteroids or antihistamine treatment. Systemic corticosteroids were used in 28 of 109 patients.

Capivasertib interruptions and reductions were reported in 42 and 16 patients, respectively, and events were mostly resolved or recovering at the time of DCO1. 16 patients (4.5%) discontinued treatment with capivasertib due to AESIs of rash.

Seven patients (2.0%) in the capivasertib + fulvestrant arm had serious AESIs of rash. Rash AESIs of CTCAE Grade 3 were reported as follows in the capivasertib + fulvestrant arm: rash maculo-papular (22 patients, 6.2%), rash (19 patients, 5.4%), and rash papular (2 patients, 0.6%).

Other selected AEs observed during CAPItello-291 within the Skin and subcutaneous tissue disorders SOC, but not captured by this AESI category include following:

Table 66 CAPItello-291: Other selected skin AEs (SAS), DCO: 15 August 2022

	Number (%) of patients			
	Capivasertib + fulvestrant (N = 355)		Placebo + fulvestrant (N = 350)	
	Total	Grade 3	Total	Grade 3
Dermatitis	3 (0.8)	0	1 (0.3)	0
Dermatitis exfoliative generalised	2 (0.6)	2 (0.6)	0	0
Drug eruption	4 (1.1)	4 (1.1)	0	0
Drug reaction with eosinophilia and systemic symptoms	1 (0.3)	0	0	0
Erythema	6 (1.7)	0	2 (0.6)	0
Erythema multiforme	6 (1.7)	3 (0.8)	0	0
Palmar-plantar erythrodysaesthesia syndrome	3 (0.8)	0	1 (0.3)	0
Rash erythematous	4 (1.1)	1 (0.3)	2 (0.6)	0
Rash follicular	1 (0.3)	0	0	0
Rash pustular	2 (0.6)	2 (0.6)	1 (0.3)	0
Toxic skin eruption	1 (0.3)	0	0	0

CTCAE Version 5.0.

MedDRA Version 25.0.

Source: Table 2.7.4.3.3, Appendix 2.7.4.7.2 in Module 5.3.5.3.

Urinary Tract Infection

The incidence of UTI AESIs was higher in the capivasertib + fulvestrant arm. Patients experiencing a UTI had a median of 1 UTI event; most were CTCAE Grade 1 or 2 and occurred during the first 4 cycles of

treatment. Most events were managed with appropriate medication. One patient in the capivasertib + fulvestrant arm discontinued treatment. Most events were recovered or recovering at the time of DCO1.

Seven patients (2.0%) in the capivasertib + fulvestrant arm had UTI AESIs of CTCAE Grade 3; in 2 patients, the UTI was reported as an SAE.

Infective Pneumonia

There was a low incidence of infective pneumonia events, and the incidence and characterisation of the events was similar in both treatment arms (2.3% vs 2.6%).

Stomatitis

The incidence of stomatitis AESIs (including PTs: aphthous ulcer, lip ulceration, mouth ulceration, mucosal inflammation, and stomatitis) was higher in the capivasertib + fulvestrant arm (20.0% vs 5.7%). Patients experiencing stomatitis had a median of 1 stomatitis event; most occurred during the first cycle of treatment, and were CTCAE Grade 1. Only few patients had dose modifications due to AESIs of stomatitis. One patient in the capivasertib + fulvestrant arm discontinued treatment due to an AESI of stomatitis. In the capivasertib + fulvestrant arm, approximately half of the patients with stomatitis required treatment. The majority of events were recovered or recovering at the time of DCO1

Stomatitis AESIs of CTCAE Grade 3 were reported in the capivasertib + fulvestrant arm as follows: stomatitis (7 patients, 2.0%) and mucosal inflammation (1 patient, 0.3%). For 1 patient (0.3%), the stomatitis was reported as a SAE.

QT Prolongation
Table 67 Characterisation of QT prolongation events (DCO: 15 August 2022)

	Number (%) of patients [a]			
	CAPItello-291		FTIH Study Pool	Combined Pool
	Capivasertib + fulvestrant (N = 355)	Placebo + fulvestrant (N = 350)	Capivasertib + fulvestrant (N = 75)	Capivasertib + fulvestrant (N = 430)
Patients experiencing QT prolongation [a]	11 (3.1)	0	5 (6.7)	16 (3.7)
Syncope	6 (1.7)	0	1 (1.3)	7 (1.6)
Electrocardiogram QT prolonged	3 (0.8)	0	4 (5.3)	7 (1.6)
Seizure	1 (0.3)	0	0	1 (0.2)
Ventricular arrhythmia	1 (0.3)	0	0	1 (0.2)
Torsade de pointes	0	0	0	0
SAEs	1 (0.3)	0	0	1 (0.2)
Maximum AE severity [b]				
CTCAE Grade 1	2 (0.6)	0	3 (4.0)	5 (1.2)
CTCAE Grade 2	1 (0.3)	0	0	1 (0.2)
CTCAE Grade 3	8 (2.3)	0	1 (1.3)	9 (2.1)
CTCAE Grade 4	0	0	1 (1.3)	1 (0.2)
CTCAE Grade 5	0	0	0	0
Median number of AEs of QT prolongation [a] per patient (IQR)	1.0 (1.0-1.0)	NC	1.0 (1.0-1.0)	1.0 (1.0-1.0)

Median time to onset in days of first AE of QT prolongation [a] per patient (IQR)	16.0 (13.0-98.0)	NC	22.0 (4.0-22.0)	17.0 (13.0-61.0)
AESI leading to capivasertib/placebo dose modification or discontinuation				
AESI leading to capivasertib/placebo dose reduction for QT prolongation [a]	0	0	0	0
AESI leading to capivasertib/placebo dose interruption for QT prolongation [a]	2 (0.6)	0	2 (2.7)	4 (0.9)
AESI leading to capivasertib/placebo discontinuation for QT prolongation [a]	0	0	0	0
Treatment required for QT prolongation [a,c]	2 (0.6)	0	0	2 (0.5)
Outcome of QT prolongation [a]: recovered/recovering [d]	10 (2.8)	0	4 (5.3)	14 (3.3)
Outcome of QT prolongation [a]: not recovered	1 (0.3)	0	1 (1.3)	2 (0.5)

[a] The QT prolongation medical concept search included the MedDRA SMQ (broad) of Torsade de pointes/QT prolongation plus the MedDRA PT of Seizure.

[b] In patients where more than one episode of event occurred, the severity represented above is on a patient-level using the highest CTCAE grade episode of event reported.

[c] According to yes/no tick box on Adverse Event CRF page.

[d] Includes terms of recovered, recovered with sequelae, and recovering. Each patient will only be counted once per category, a patient will be counted in more than one category if the outcomes are different.

Percentages are based on the total number of patients in the treatment group (N).
CTCAE Version 4.0 was used in the FTIH study (D3610C00001) and Version 5.0 in CAPItello-291. MedDRA Version 25.0.

Other AEs of potential interest

Renal Function-related Adverse Events

Table 68 Renal function-related adverse events (SAS), DCO: 15 August 2022

	Number (%) of patients			
	Capivasertib + Fulvestrant (N = 355)		**Placebo + Fulvestrant (N = 350)**	
	Total	**Grade 3**	**Total**	**Grade 3**
Acute kidney injury	5 (1.4)	3 (0.8)	0	0
Renal failure	2 (0.6)	1 (0.3)	1 (0.3)	0
Renal impairment	4 (1.1)	0	1 (0.3)	1 (0.3)
Blood creatinine increased	16 (4.5)	1 (0.3)	2 (0.6)	0

Hepatic AEs

Grade 3 hepatic AEs were reported as follows: AST increased (7 patients in each treatment arm), ALT increased (capivasertib + fulvestrant, 7 patients; placebo + fulvestrant, 3 patients), blood ALP increased (capivasertib + fulvestrant, 2 patients), γ-glutamyl transferase (GGT) increased (1 patient in each treatment arm), hepatic enzyme increased (placebo + fulvestrant, 1 patient), and drug-induced liver injury (1 patient in each treatment arm).

Adverse drug reactions

The primary safety population from the pivotal placebo-controlled CAPItello-291 study was considered the most appropriate basis for identification of ADRs. Objective criteria were applied to the data for AEs to screen for potential ADRs, which were then subject to clinical review. Based on the analysis, the ADRs, as summarised in the ADR Table were identified for capivasertib in the CAPItello-291 study. This approach however was modified/updated to include data from patients treated with capivasertib plus fulvestrant in clinical studies at the recommended dose (including FTIH Study Pool and FAKTION study). Furthermore, all AEs for which a causal relationship to the capivasertib treatment has been established are now included in ADR table.

Table 69 ADRs, by system organ class and ADR grouped term; DCO: 15-08-2022

	Capitello - 291				D3610C00001		Total	
	Capivasertib + Fulvestrant (N=355)		Placebo + Fulvestrant (N=350)		Capivasertib + Fulvestrant (N=75)		Capivasertib + Fulvestrant (N=430)	
System Organ Class/ ADR grouped term	Number (%) of patients [a]	CIOMS III category [b]	Number (%) of patients [a]	CIOMS III category [b]	Number (%) of patients [a]	CIOMS III category [b]	Number (%) of patients [a]	CIOMS III category [b]
Patients with any ADR	325 (91.5)		189 (54.0)		72 (96.0)		397 (92.3)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	37 (10.4)		17 (4.9)		10 (13.3)		47 (10.9)	
Anaemia	37 (10.4)	Very Common	17 (4.9)	Common	10 (13.3)	Very Common	47 (10.9)	Very Common
GASTROINTESTINAL DISORDERS	288 (81.1)		123 (35.1)		67 (89.3)		355 (82.6)	
Diarrhoea	257 (72.4)	Very Common	70 (20.0)	Very Common	49 (65.3)	Very Common	306 (71.2)	Very Common
Nausea	123 (34.6)	Very Common	54 (15.4)	Very Common	37 (49.3)	Very Common	160 (37.2)	Very Common
Vomiting	73 (20.6)	Very Common	17 (4.9)	Common	20 (26.7)	Very Common	93 (21.6)	Very Common
Stomatitis	61 (17.2)	Very Common	19 (5.4)	Common	12 (16.0)	Very Common	73 (17.0)	Very Common
Dyspepsia	18 (5.1)	Common	7 (2.0)	Common	1 (1.3)	Common	19 (4.4)	Common
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	81 (22.8)		46 (13.1)		17 (22.7)		98 (22.8)	
Fatigue	74 (20.8)	Very Common	45 (12.9)	Very Common	17 (22.7)	Very Common	91 (21.2)	Very Common
Mucosal inflammation	11 (3.1)	Common	1 (0.3)	Uncommon	0		11 (2.6)	Common
IMMUNE SYSTEM DISORDERS	3 (0.8)		0		1 (1.3)		4 (0.9)	
Hypersensitivity	3 (0.8)	Uncommon	0		1 (1.3)	Common	4 (0.9)	Uncommon
INFECTIONS AND INFESTATIONS	48 (13.5)		24 (6.9)		9 (12.0)		57 (13.3)	
Urinary Tract Infection	48 (13.5)	Very Common	24 (6.9)	Common	9 (12.0)	Very Common	57 (13.3)	Very Common
INVESTIGATIONS	21 (5.9)		2 (0.6)		5 (6.7)		26 (6.0)	
Blood Creatinine increased	16 (4.5)	Common	2 (0.6)	Uncommon	4 (5.3)	Common	20 (4.7)	Common
Glycosylated haemoglobin increased	5 (1.4)	Common	0		1 (1.3)	Common	6 (1.4)	Common
METABOLISM AND NUTRITION DISORDERS	113 (31.8)		33 (9.4)		27 (36.0)		140 (32.6)	
Decreased appetite	59 (16.6)	Very Common	22 (6.3)	Common	18 (24.0)	Very Common	77 (17.9)	Very Common
Hyperglycaemia	60 (16.9)	Very Common	14 (4.0)	Common	16 (21.3)	Very Common	76 (17.7)	Very Common
NERVOUS SYSTEM DISORDERS	21 (5.9)		4 (1.1)		3 (4.0)		24 (5.6)	
Dysgeusia	21 (5.9)	Common	4 (1.1)	Common	3 (4.0)	Common	24 (5.6)	Common
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	183 (51.5)		55 (15.7)		31 (41.3)		214 (49.8)	
Rash	143 (40.3)	Very Common	29 (8.3)	Common	28 (37.3)	Very Common	171 (39.8)	Very Common

Pruritus	44 (12.4)	Very Common	23 (6.6)	Common	10 (13.3)	Very Common	54 (12.6)	Very Common
Dry skin	25 (7.0)	Common	15 (4.3)	Common	5 (6.7)	Common	30 (7.0)	Common
Erythema multiforme	6 (1.7)	Common	0		0		6 (1.4)	Common
Drug Eruption	4 (1.1)	Common	0		0		4 (0.9)	Uncommon
Dermatitis	3 (0.8)	Uncommon	1 (0.3)	Uncommon	0		3 (0.7)	Uncommon
Dermatitis exfoliative generalised	2 (0.6)	Uncommon	0		0		2 (0.5)	Uncommon
Toxic Skin Eruption	1 (0.3)	Uncommon	0		0		1 (0.2)	Uncommon

Table 70 ADRs CTCAE grade 3 or higher, by system organ class and ADR grouped term; DCO: 15 August 2022

	Number(%) of patients [a]							
	Capitello - 291				D3610C00001		Total	
System Organ Class/ ADR grouped term	Capivasertib + Fulvestrant (N=365)	CIOMS III category [b]	Placebo + Fulvestrant (N=350)	CIOMS III category [b]	Capivasertib + Fulvestrant (N=75)	CIOMS III category [b]	Capivasertib + Fulvestrant (N=430)	CIOMS III category [b]
INFECTIONS AND INFESTATIONS	6 (1.7)		0		1 (1.3)		7 (1.6)	
Urinary Tract Infection	6 (1.7)	Common	0		1 (1.3)	Common	7 (1.6)	Common
INVESTIGATIONS	1 (0.3)		0		0		1 (0.2)	
Blood Creatinine increased	1 (0.3)	Uncommon	0		0		1 (0.2)	Uncommon
METABOLISM AND NUTRITION DISORDERS	8 (2.3)		3 (0.9)		4 (5.3)		12 (2.8)	
Hyperglycaemia	8 (2.3)	Common	1 (0.3)	Uncommon	4 (5.3)	Common	12 (2.8)	Common
Decreased appetite	1 (0.3)	Uncommon	2 (0.6)	Uncommon	1 (1.3)	Common	2 (0.5)	Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	54 (15.2)		2 (0.6)		8 (10.7)		62 (14.4)	
Dry skin	0		1 (0.3)	Uncommon	0		0	
Rash	44 (12.4)	Very Common	1 (0.3)	Uncommon	8 (10.7)	Very Common	52 (12.1)	Very Common
Drug Eruption	4 (1.1)	Common	0		0		4 (0.9)	Uncommon
Patients with ADR of any CTCAE grade 3 or higher	100 (28.2)		11 (3.1)		20 (26.7)		120 (27.9)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	7 (2.0)		4 (1.1)		1 (1.3)		8 (1.9)	
Anaemia	7 (2.0)	Common	4 (1.1)	Common	1 (1.3)	Common	8 (1.9)	Common
GASTROINTESTINAL DISORDERS	45 (12.7)		3 (0.9)		8 (10.7)		53 (12.3)	
Diarrhoea	33 (9.3)	Common	1 (0.3)	Uncommon	4 (5.3)	Common	37 (8.6)	Common
Vomiting	6 (1.7)	Common	2 (0.6)	Uncommon	2 (2.7)	Common	8 (1.9)	Common
Stomatitis	7 (2.0)	Common	0		0		7 (1.6)	Common
Nausea	3 (0.8)	Uncommon	2 (0.6)	Uncommon	3 (4.0)	Common	6 (1.4)	Common
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (0.8)		2 (0.6)		1 (1.3)		4 (0.9)	
Fatigue	2 (0.6)	Uncommon	2 (0.6)	Uncommon	1 (1.3)	Common	3 (0.7)	Uncommon
Mucosal inflammation	1 (0.3)	Uncommon	0		0		1 (0.2)	Uncommon
Erythema multiforme	3 (0.8)	Uncommon	0		0		3 (0.7)	Uncommon
Dermatitis exfoliative generalised	2 (0.6)	Uncommon	0		0		2 (0.5)	Uncommon
Pruritus	2 (0.6)	Uncommon	0		0		2 (0.5)	Uncommon

Table 71 Serious adverse drug reactions, by system organ class and ADR grouped term DCO: 15 August 2022

	Capitello - 291				D3610C00001		Total	
	Capivasertib + Fulvestrant (N=355)		Placebo + Fulvestrant (N=350)		Capivasertib + Fulvestrant (N=75)		Capivasertib + Fulvestrant (N=430)	
System Organ Class/ ADR grouped term	Number (%) of patients [a]	CIOMS III category [b]	Number (%) of patients [a]	CIOMS III category [b]	Number (%) of patients [a]	CIOMS III category [b]	Number (%) of patients [a]	CIOMS III category [b]
Patients with any Serious ADR	23 (6.5)		4 (1.1)		8 (10.7)		31 (7.2)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0		1 (0.3)		0		0	
Anaemia	0		1 (0.3)	Uncommon	0		0	
GASTROINTESTINAL DISORDERS	11 (3.1)		3 (0.9)		4 (5.3)		15 (3.5)	
Vomiting	4 (1.1)	Common	2 (0.6)	Uncommon	3 (4.0)	Common	7 (1.6)	Common
Diarrhoea	6 (1.7)	Common	1 (0.3)	Uncommon	0		6 (1.4)	Common
Nausea	1 (0.3)	Uncommon	2 (0.6)	Uncommon	2 (2.7)	Common	3 (0.7)	Uncommon
Stomatitis	1 (0.3)	Uncommon	0		0		1 (0.2)	Uncommon
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.3)		0		0		1 (0.2)	
Fatigue	1 (0.3)	Uncommon	0		0		1 (0.2)	Uncommon
IMMUNE SYSTEM DISORDERS	1 (0.3)		0		0		1 (0.2)	
Hypersensitivity	1 (0.3)	Uncommon	0		0		1 (0.2)	Uncommon
INFECTIONS AND INFESTATIONS	1 (0.3)		0		2 (2.7)		3 (0.7)	
Urinary Tract Infection	1 (0.3)	Uncommon	0		2 (2.7)	Common	3 (0.7)	Uncommon
METABOLISM AND NUTRITION DISORDERS	3 (0.8)		0		1 (1.3)		4 (0.9)	
Hyperglycaemia	3 (0.8)	Uncommon	0		1 (1.3)	Common	4 (0.9)	Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	11 (3.1)		0		1 (1.3)		12 (2.8)	
Rash	8 (2.3)	Common	0		1 (1.3)	Common	9 (2.1)	Common
Dermatitis exfoliative generalised	1 (0.3)	Uncommon	0		0		1 (0.2)	Uncommon
Drug Eruption	1 (0.3)	Uncommon	0		0		1 (0.2)	Uncommon
Erythema multiforme	1 (0.3)	Uncommon	0		0		1 (0.2)	Uncommon

[a] Number (%) of patients with Serious ADRs, sorted by system organ class and descending frequency for ADR grouped term (Capivasertib + Fulvestrant group in the capi-291 study).
[b] CIOMS III convention and is defined as: (1) very common (>= 1/10), (2) common (> =1/100 to < 1/10), (3) uncommon (>= 1/1,000 to < 1/100), (4) rare (>= 1/10,000 to < 1/1,000), (5) very rare (< 1/10,000), and (6) NK (not known -cannot be estimated from available data)
Note: Includes for CAPItello-291 - Serious ADRs with an onset date on/after date of first dose. ADRs with onset date prior to dosing which worsen after dosing and ADRs occurring up to 30 days (+7 days) following date of last dose.
Note: Includes for D3610C00001 - ADRs with onset date on or after the date of first dose and up to 28 days following date of last dose. AE worsening (CTCAE grade change) data not collected in this study.
Percentages are based on the total number of patients in the treatment group (N).
Serious ADR = Serious Adverse drug reactions. MedDRA version 25.0.
root/cdar/d3361/ sub capi291/ar/ias ia/tlf/prod/program/t aesi005a.sas t aesi005a.rtf 17FEB2023:13:07 klnx332

Upon CHMP request, the following ADRs were included in section 4.8 of the SmPC: asthenia (in the footnote, as part of fatigue), pyrexia (common), headache (very common), dry mouth (common), abdominal pain (common), hypokalaemia (common), dizziness (common), acute kidney injury (common), and syncope (common).

2.6.8.1. Serious adverse event/deaths/other significant events

Deaths

Table 72 Summary of deaths (SAS)

Category	Number (%) of patients			
	CAPItello-291		FTIH Study Pool	Combined Pool
	Capivasertib + fulvestrant (N = 355)	Placebo + fulvestrant (N = 350)	Capivasertib + fulvestrant (N = 75)	Capivasertib + fulvestrant (N = 430)
Total number of deaths	87 (24.5)	107 (30.6)	48 (64.0)	135 (31.4)
Death related to disease under investigation only [a]	79 (22.3)	101 (28.9)	43 (57.3)	122 (28.4)
AE with outcome of death only [b]	4 (1.1)	1 (0.3)	0	4 (0.9)
AE with outcome of death and death related to disease under investigation [b]	0	0	0	0
AE with outcome of death and AE onset date falling after 30 (+ 7) days following the last dose of study treatment [c]	1 (0.3)	0	0	1 (0.2)
Other deaths [d]	3 (0.8)	5 (1.4)	5 (6.7)	8 (1.9)

[a] Death related to disease under investigation as determined by the investigator.

[b] AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing; AEs occurring up to 30 days (+ 7 days) following date of last dose are reported.

[c] Investigators were not obligated to actively seek AEs in patients who had already completed follow-up. The AE reported in this category had the PT General physical health deterioration and was not considered related to treatment.

[d] Patients who died and are not captured in the earlier categories. Investigators were not obligated to actively seek AEs in patients who had already completed follow-up. This category includes deaths that occurred after follow-up had been completed, were not reported as AEs, and were not only related to the disease under investigation.

At the DCO 27 March 2023, one additional death was reported in the category 'AE with outcome of death only' in the capivasertib + fulvestrant arm. The event of Liver abscess was assessed by the investigator as possibly related to capivasertib.

Table 73 Adverse events with an outcome of death by PT (CAPItello 291-SAS)

MedDRA preferred term	Number (%) of patients	
	Capivasertib + Fulvestrant (N = 355)	Placebo + Fulvestrant (N = 350)
Patients with AE with outcome of death	4 (1.1)	1 (0.3)
Acute myocardial infarction	1 (0.3)	0
Cerebral haemorrhage	1 (0.3)	0
Liver abscess	1 (0.3)	0
Pneumonia aspiration	1 (0.3)	0
Sepsis	1 (0.3)	0
COVID-19	0	1 (0.3)

Patients with multiple events in the same preferred term are counted only once in that preferred term.

Note: AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing; AEs occurring up to 30 days (+ 7 days) following date of last dose are reported.
Percentages are based on the total number of patients in the treatment arm
(N). MedDRA version 25.0

Serious Adverse Events

Table 74 SAEs (reported in ≥ 2 capivasertib-treated patients in CAPItello-291) by PT (SAS)

MedDRA PT	Number (%) of patients [a]			
	CAPItello-291		FTIH Study Pool	Combined Pool
	Capivasertib + fulvestrant (N = 355)	Placebo + fulvestrant (N = 350)	Capivasertib + fulvestrant (N = 75)	Capivasertib + fulvestrant (N = 430)
Patients with any SAE[c]	62 (17.5)	28 (8.0)	24 (32.0)	86 (20.0)
Diarrhoea[c]	9 (2.5)	1 (0.3)	0	9 (2.1)
Rash maculo-papular [b]	5 (1.4)	0	1 (1.3)	6 (1.4)
Vomiting	4 (1.1)	2 (0.6)	3 (4.0)	7 (1.6)
Acute kidney injury[c]	4 (1.1)	0	0	4 (1.0)
Hyperglycaemia	3 (0.8)	0	1 (1.3)	4 (0.9)
Asthenia	2 (0.6)	0	0	2 (0.5)
Pneumonia aspiration	2 (0.6)	0	0	2 (0.5)
Sepsis	2 (0.6)	1 (0.3)	0	2 (0.5)
COVID-19[c]	2 (0.6)	1 (0.3)		
Pyelonephritis[c]	2 (0.6)	0		
Stomatitis[c]	2 (0.6)	0		

[a] Number (%) of patients with SAEs, sorted in descending frequency of PT in the capivasertib + fulvestrant arm of CAPItello-291.

[b] This PT is included in the AESI grouped term of rash.

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[c] Update of the table with SAEs reported at the 27 March 2023 DCO

2.6.8.2. Laboratory findings

Haematology

In CAPItello-291, there were more clinically relevant decreases in haemoglobin and lymphocytes in the capivasertib + fulvestrant arm than in the placebo + fulvestrant arm.

For haemoglobin, there was a higher proportion of patients with a CTCAE grade shift (decrease) in the capivasertib + fulvestrant arm (44.9%) than in the placebo + fulvestrant arm (21.0%); most had a maximum increase of one grade (41.2% and 17.5%, respectively), and most shifts were from CTCAE Grade 0 to Grade 1.

For lymphocytes, there was a higher proportion of patients with a CTCAE grade shift (decrease) in the capivasertib + fulvestrant arm (46.3%) than in the placebo + fulvestrant arm (18.1%); almost half of those in the capivasertib + fulvestrant arm had a maximum decrease of more than one grade.

Clinical Chemistry

In CAPItello-291, for sodium, there was a higher proportion of patients with a CTCAE grade shift (increase) in the capivasertib + fulvestrant arm (7.9%) than in the placebo + fulvestrant arm (4.3%). There were no high sodium results above CTCAE Grade 1. There was no significant impact on patients.

In CAPItello-291, for potassium, there was a higher proportion of patients with a CTCAE grade shift (decrease) in the capivasertib + fulvestrant arm (16.7%) than in the placebo + fulvestrant arm (4.9%); most had a maximum increase of one grade (13.3% and 4.6%, respectively). Decreased potassium is possibly a secondary consequence of diarrhoea.

There was a higher proportion of patients with a grade shift in calcium (corrected for albumin) (increase) in the capivasertib + fulvestrant arm (15.6%) compared with the placebo + fulvestrant arm (7.8%); most had a maximum decrease of 1 grade (13.3% and 7.8%, respectively)

There were shifts in urea from normal at baseline to above the ULN during the study in 33.5% of patients in the capivasertib + fulvestrant arm compared with 15.5% of patients in the placebo + fulvestrant arm.

There was a higher proportion of patients with a grade shift in magnesium (decrease) in the capivasertib + fulvestrant arm (5.7%) compared with the placebo + fulvestrant arm (1.2%); most had a maximum decrease of 1 grade (5.1% and 1.2%, respectively).

Lipids

Similar proportions of patients in the capivasertib + fulvestrant arm and the placebo + fulvestrant arm had a shift in total cholesterol and LDL cholesterol from within the normal range at baseline to above the ULN during treatment (total cholesterol: 27.1% and 27.3%, respectively; LDL cholesterol: 22.1% and 24.2%, respectively).

There was a slightly higher proportion of patients in the capivasertib + fulvestrant arm with a shift in triglycerides from within the normal range at baseline to above the ULN during treatment, compared with the placebo + fulvestrant arm (27.8% vs 20.5%)

Renal Biochemistry

In CAPItello-291, there was a higher proportion of patients with a CTCAE grade shift (increase) in creatinine in the capivasertib + fulvestrant arm (21.8%) than in the placebo + fulvestrant arm (6.3%).

In CAPItello-291 in the capivasertib + fulvestrant arm, there was a small increase in median creatinine at Cycle 1 (66.3 µmol/L versus 63.6 µmol/L at baseline), though it remained stable and well within the normal range for the duration of the on-treatment period.

Hepatic Biochemistry

In CAPItello-291, there were lower proportions of patients with CTCAE grade shifts (increases) in AST and alkaline phosphatase in the capivasertib + fulvestrant arm than in the placebo + fulvestrant arm; maximum grade shifts in ALT and bilirubin were similar between the 2 arms.

There were cases of potential Hy's Law (10 in the capivasertib + fulvestrant arm and 14 in the placebo + fulvestrant arm) reported but all had alternative explanation for the elevation in liver biochemistry other than study treatment (i.e. progression of disease).

Urinalysis

There were more shifts from negative at baseline to trace or positive urine glucose results on treatment in the capivasertib + fulvestrant arm compared with the placebo + fulvestrant arm, which was expected.

Vital Signs

There were no unexpected or clinically meaningful trends or changes from baseline in vital signs over time.

ECG

In the CAPitello 291 study, most of the ECGs recorded during the study were 'normal' or 'abnormal but not clinically significant' as reported by the investigator. However, there were slightly more "abnormal - clinically significant' observations in the capivasertib + fulvestrant arm than in placebo + fulvestrant arm (1.9% vs 0.3%).

Overall, reported changes from baseline in the mean or median QTc interval were small; and both very small increases and decreases were observed, and were similar in both treatment arms. The mean and median increase in QTc interval from baseline at 1 hour post-dose (Cycle 1, Week 1, Day 1), close to the time of expected peak concentration for capivasertib, were less than 1 msec.

The proportion of patients with QTcF increases of > 30 msec from baseline at any time during treatment was 7.9% in the capivasertib + fulvestrant arm and 5.7% in the placebo + fulvestrant arm. Few patients had a change from baseline of > 60 msec and this was balanced between the arms (2 patients [0.6%] in the capivasertib + fulvestrant arm, 3 patients [0.9%] in the placebo + fulvestrant arm). One patient in the capivasertib + fulvestrant arm had a QTcF value above 500 msec whilst on treatment. Adverse events related to QT prolongation were discussed previously.

2.6.8.3. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.4. Safety in special populations

Intrinsic factors

Effect of Age

Table 75 Key safety parameters by age group (CAPItello-291-SAS)

	Number (%) of Patients [a]							
	Capivasertib + Fulvestrant				Placebo + Fulvestrant			
	< 65 Years (N = 240)	65 to 74 Years (N = 91)	75 to 84 Years (N = 24)	≥ 85 Years (N = 0)	< 65 Years (N = 249)	65 to 74 Years (N = 76)	75 to 84 Years (N = 23)	≥ 85 Years (N = 2)
Total AEs	231 (96.3)	89 (97.8)	23 (95.8)	0	202 (81.1)	66 (86.8)	18 (78.3)	2 (100)
Serious AEs - total	35 (14.6)	18 (19.8)	4 (16.7)	0	20 (8.0)	7 (9.2)	0	1 (50.0)
Fatal	3 (1.3)	0	1 (4.2)	0	1 (0.4)	0	0	0
Hospitalisation/prolong existing hospitalisation	31 (12.9)	18 (19.8)	4 (16.7)	0	15 (6.0)	6 (7.9)	0	1 (50.0)
Life-threatening	3 (1.3)	2 (2.2)	0	0	4 (1.6)	1 (1.3)	0	0
Disability/incapacity	1 (0.4)	1 (1.1)	0	0	2 (0.8)	1 (1.3)	0	1 (50.0)
Other (medically significant)	8 (3.3)	6 (6.6)	0	0	5 (2.0)	1 (1.3)	0	0
AE leading to discontinuation of capivasertib/placebo	20 (8.3)	20 (22.0)	6 (25.0)	0	7 (2.8)	0	0	1 (50.0)
Psychiatric disorders (SOC)	22 (9.2)	8 (8.8)	3 (12.5)	0	21 (8.4)	8 (10.5)	3 (13.0)	1 (50.0)
Nervous system disorders (SOC)	73 (30.4)	31 (34.1)	8 (33.3)	0	61 (24.5)	15 (19.7)	3 (13.0)	0
Injury, poisoning and procedural complications (SOC)	12 (5.0)	7 (7.7)	3 (12.5)	0	8 (3.2)	4 (5.3)	2 (8.7)	0
Cardiac disorders (SOC)	13 (5.4)	8 (8.8)	3 (12.5)	0	5 (2.0)	3 (3.9)	1 (4.3)	1 (50.0)
Vascular disorders (SOC)	27 (11.3)	14 (15.4)	4 (16.7)	0	31 (12.4)	7 (9.2)	3 (13.0)	1 (50.0)
Infections and infestations (SOC)	79 (32.9)	35 (38.5)	10 (41.7)	0	51 (20.5)	9 (11.8)	7 (30.4)	1 (50.0)
Cerebrovascular disorders (SMQ) [b]	2 (0.8)	1 (1.1)	1 (4.2)	0	0	0	0	0
Anticholinergic syndrome (PT)	0	0	0	0	0	0	0	0
Quality of life decreased (PT)	0	0	0	0	0	0	0	0
Sum of postural hypotension, fall, loss of consciousness, syncope, dizziness, ataxia, and fracture	12 (5.0)	10 (11.0)	3 (12.5)	0	11 (4.4)	3 (3.9)	0	0

Effect of Sex

Although breast cancer is a disease occurring largely in the female population, 3 (0.7%) patients in the Combined Pool were male (all from CAPItello-291). In the Monotherapy Pool, 31 (18.8%) patients were male.

Effect of Race

The overall incidence of AEs, SAEs, and AESIs in the capivasertib + fulvestrant arm of CAPItello-291 was similar across the 2 largest race subgroups (White [N = 201] and Asian [N = 95]). The incidence of CTCAE Grade 3 or higher AEs was higher in the Asian group (48.4%) than in the White group (39.3%). The types of AEs most commonly reported were similar between the race subgroups.

Effect of Weight

The overall incidence of AEs in the capivasertib + fulvestrant arm of CAPItello-291 was generally similar across the weight subgroups (baseline weight < 50 kg [N = 35], ≥ 50 to < 70 kg [N = 184], ≥ 70 to < 90 kg [N = 101], and ≥ 90 kg [N = 31]).

The types of AEs most commonly reported were similar between the weight subgroups.

The incidence of SAEs was higher in the baseline weight < 50 kg group (25.7%) than in the other groups (≥ 50 to < 70 kg, 16.3%; ≥ 70 to < 90 kg, 12.9%; ≥ 90 kg, 16.1%). The incidence of CTCAE Grade 3 or higher AEs was higher in the baseline weight < 50 kg group (54.3%) than in the other groups (≥ 50 to < 70 kg, 44.0%; ≥ 70 to < 90 kg, 35.6%; ≥ 90 kg, 41.9%).

The incidence of AEs leading to dose reduction of capivasertib was also higher in the baseline weight < 50 kg group (37.1%) than in the other groups (≥ 50 to < 70 kg, 21.7%; ≥ 70 to < 90 kg, 10.9%; ≥ 90 kg, 9.7%).

Effect of PIK3CA/AKT1/PTEN Alteration Status

Altered population is molecularly defined subgroup with tumours harbouring at least 1 PIK3CA/AKT1/PTEN-qualifying alteration detected in tissue.

The overall incidence of AEs, CTCAE Grade 3 or higher AEs, SAEs, and AESIs in CAPItello-291 was similar between the alteration status subgroups. The types of AEs most commonly reported were also similar between subgroups. The most commonly reported AEs (≥ 20% of patients, by PT) in the capivasertib + fulvestrant arm of CAPItello-291 were as follows:

- Altered (N = 155): Diarrhoea (76.8%), Nausea (34.8%), Fatigue (22.6%), Rash maculo-papular and Vomiting (20.6% each), and Rash (20.0%)
- Confirmed non-altered (N = 142): Diarrhoea (68.3%), Nausea (33.1%), Rash (24.6%), and Vomiting (21.8%)
- Non-altered + unknown (N = 58): Diarrhoea (70.7%), Nausea (37.9%), Fatigue (22.4%), and Decreased appetite, Hyperglycaemia, and Rash (20.7% each).

The incidence of AEs leading to discontinuation of capivasertib was higher in the confirmed non-altered group (16.9%) than in the confirmed altered group (10.3%) or the non-altered + unknown group (10.3%) and a total duration of exposure to capivasertib/placebo in confirmed non-altered group was shorter than in altered or non-altered + unknown group (3.6, 6.3 and 7.3 months, respectively).

Effect of WHO/ECOG PS

The overall incidence of AEs, CTCAE Grade 3 or higher AEs, and AESIs was similar between the WHO/ECOG PS subgroups, however, incidence of SAEs was higher in the WHO/ECOG PS ≥ 1 group (22.1%) than in the WHO/ECOG PS 0 group (12.3%).

Effect of HbA1C at Baseline and Medical History of Diabetes Mellitus

The patients with controlled diabetes type II could be included in the CAPItello-291, however with HbA1C< 8% at baseline. At baseline in CAPItello-291, 34 (9.6%) patients in the capivasertib + fulvestrant arm and 20 (5.7%) patients in the placebo + fulvestrant arm had diabetes mellitus.

Considering the small number of patients with a baseline HbA1C ≥ 6.5% (N = 21, CAPItello-291) and only 5.9% of patients in the capivasertib + fulvestrant arm of CAPItello-291, the assessment of the capivasertib's safety profile by these factors should be interpreted with caution.

The overall incidence of AEs was similar between the HbA1C subgroups (97% in the HbA1C < 6.5% group and 90.5% in the HbA1C ≥ 6.5% group, as well as between the subgroups with and without a medical history of diabetes mellitus.

The incidences of CTCAE Grade 3 or higher AEs (66.7% versus 41.6%) and SAEs (28.6% versus 15.4%) were higher in the HbA1C ≥ 6.5% group than in the HbA1C < 6.5% group and also in the medical history of diabetes mellitus group (58.8% versus 41.1% and 23.5% vs 15.3%, respectively).

The overall incidence of AESIs was higher in the HbA1C < 6.5% group (88.3%) than in the HbA1C ≥ 6.5% group (76.2%).

AEs of Hyperglycaemia (PT) were more frequently reported in patients with a baseline HbA1C ≥ 6.5% (6 [28.6%] patients) than those with a baseline HbA1C < 6.5% (51 [15.4%] patients), and also in patients with a medical history of diabetes mellitus (10 [29.4%] patients) than those without a history of diabetes mellitus (48 [15.0%] patients).

AEs of Diabetic ketoacidosis, Diabetes mellitus, and Diabetic metabolic decompensation were reported in one (4.8%) patient each in the HbA1C ≥ 6.5% subgroup. An AE of Diabetic metabolic decompensation was reported in one (0.3%) patient in the HbA1C < 6.5% subgroup.

AEs of Diabetic ketoacidosis and Diabetic metabolic decompensation were reported in one (2.9%) patient each in the subgroup with a medical history of diabetes mellitus.

AEs of Diabetes mellitus and Diabetic metabolic decompensation were reported in one (0.3%) patient each in the subgroup without a medical history of diabetes mellitus.

Effect of Menopausal Status

The overall incidence of AEs, SAEs, and AESIs was similar between the pre-/peri-menopausal group and the post-menopausal group.

The incidence of CTCAE Grade 3 or higher AEs was higher in the post-menopausal group (45.6%) than in the pre-/peri-menopausal group (30.8%). The types of AEs most commonly reported were similar between the menopausal status subgroups.

Some differences in incidence of AEs between pre-/peri-menopausal and post-menopausal women may be attributed to variables such as age and use of luteinising hormone-releasing hormone agonists in the former.

Extrinsic factor

Effect of Prior Use of CDK4/6 Inhibitors

The overall incidence of AEs, CTCAE Grade 3 or higher AEs, SAEs, and AESIs was similar between the groups with and without prior use of CDK4/6 inhibitors. The types of AEs most commonly reported were similar between patients with or without prior use of CDK4/6 inhibitors.

Overdose

Table 76 CAPItello-291: Capivasertib or placebo overdose characterisation (SAS)

		Capivasertib + fulvestrant (N = 355)	Placebo + fulvestrant (N = 350)
Number of patients (%) experiencing an overdose with capivasertib/placebo		58 (16.3)	50 (14.3)
Number of patients (%) with an overdose associated with an AE		1 (0.3)	0
Number of overdoses per patient	Mean (SD)	2.0 (1.96)	1.6 (1.14)
	Median	1.0	1.0
	Min, max	1, 12	1, 6
Number of overdoses per patient, n (%)	1	36 (62.1)	33 (66.0)
	2	11 (19.0)	11 (22.0)
	3	4 (6.9)	1 (2.0)
	⩾ 4	7 (12.1)	5 (10.0)

2.6.8.5. Immunological events

Not applicable.

2.6.8.6. Safety related to drug-drug interactions and other interactions

Please refer to the assessment of clinical pharmacology.

2.6.8.7. Discontinuation and dose modification due to adverse events

Table 77 CAPItello-291, FTIH study pool, and combined pool: AEs leading to discontinuation of capivasertib/placebo (reported in ≥ 2 capivasertib-treated patients in CAPItello-291) by PT (SAS)

MedDRA PT	Number (%) of patients [a]			
	CAPItello-291		FTIH Study Pool	Combined Pool
	Capivasertib + fulvestrant (N = 355)	Placebo + fulvestrant (N = 350)	Capivasertib + fulvestrant (N = 75)	Capivasertib + fulvestrant (N = 430)
Patients with any AE leading to discontinuation of capivasertib/placebo	46 (13.0)	8 (2.3)	6 (8.0)	52 (12.1)
Rash [b]	11 (3.1)	0	0	11 (2.6)
Diarrhoea	7 (2.0)	0	0	7 (1.6)
Vomiting	7 (2.0)	2 (0.6)	0	7 (1.6)
Rash maculo-papular [b]	5 (1.4)	0	1 (1.3)	6 (1.4)
Pyrexia	4 (1.1)	0	0	4 (0.9)

Alanine aminotransferase increased	3 (0.8)	0	0	3 (0.7)
Aspartate aminotransferase increased	3 (0.8)	1 (0.3)	0	3 (0.7)
Nausea	3 (0.8)	1 (0.3)	0	3 (0.7)
Acute kidney injury	2 (0.6)	0	0	2 (0.5)
Drug eruption	2 (0.6)	0	0	2 (0.5)
Paraesthesia	2 (0.6)	0	0	2 (0.5)
Sepsis	2 (0.6)	0	0	2 (0.5)
Urticaria	2 (0.6)	0	0	2 (0.5)

[a] Number (%) of patients with AEs leading to discontinuation of capivasertib/placebo, sorted in descending frequency of PT in the capivasertib + fulvestrant arm of CAPItello-291.

[b] These PTs are included in the AESI grouped term of rash.

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Adverse events leading to dose modifications

In the safety analysis set of the CAPItello 291 study, the incidence of AEs leading to dose modifications of capivasertib/placebo was higher in the capivasertib + fulvestrant arm (43.9%) compared with the placebo + fulvestrant arm (12.3%).

More patients in the capivasertib arm had dose reductions (30.7%) and dose interruptions (50.7%) in comparison to placebo (6.9% and 22.9%, respectively). Adverse events were the most common reason for the dose reductions, interruptions and delays (only fulvestrant) in both treatment arms.

The incidence of AEs leading to dose interruptions of capivasertib/placebo only was 34.9% in the capivasertib + fulvestrant arm and 10.3% in the placebo + fulvestrant arm. The AEs most commonly leading to dose interruptions of capivasertib were diarrhoea (9%), rash maculo-papular (6.2%), rash (4.2%), vomiting (3.1%), hyperglycaemia(2.5%), and nausea (2.3%).

The incidence of AEs leading to dose reductions of capivasertib/placebo only was higher in the capivasertib + fulvestrant arm (19.7%) compared with the placebo + fulvestrant arm (1.7%). The AEs most commonly leading to dose reductions were diarrhoea (7.9%), rash maculo-papular (2.5%), vomiting (1.7%), and rash and nausea (1.4% each). The majority of patients reached a stable dose within 2 months of starting treatment.

2.6.8.8. Post marketing experience

Capivasertib was approved in US on 16 November 2023; however, no post-marketing data are available.

2.6.9. Discussion on clinical safety

The evaluation of safety is based on data from clinical studies in patients treated with capivasertib in combination with fulvestrant, and supported by data from capivasertib monotherapy studies. Overall, 664 patients are included in the safety database. Although limited, the size of the safety database is considered sufficient for an assessment of the safety profile of capivasertib in the proposed advanced metastatic setting. The primary safety population includes 355 patients from CAPItello-291 and provides the pivotal safety data to evaluate the safety and tolerability of capivasertib + fulvestrant in the target population.

Median total treatment duration was longer in the capivasertib + fulvestrant arm (capivasertib 5.42 months, fulvestrant 5.75 months) than in the placebo + fulvestrant arm (placebo 3.58 months,

fulvestrant 3.68 months). Of note, the comparison with the median actual treatment duration, 5.3 months for the capivasertib + fulvestrant arm and 3.5 months for the placebo + fulvestrant arm, suggests that administration interruptions had a limited impact on the overall course of the treatment in both arms. The median relative dose intensity of capivasertib was high (93.8%) and this despite dose modifications, including dose interruptions in half of the patients in the capivasertib + fulvestrant arm, which indicates that these interruptions were not long.

However, only about half of the patients (52.4%) were exposed to the study treatment for at least 6 months and 27.0% for at least 12 months. The censored data show that 70.1% of the patients of the capivasertib + fulvestrant arm and 60.9% in the placebo + fulvestrant arm are still in survival follow up at the first data cut-off (DCO1: 15-08-2022).

With the updated safety data, based on the latest DCO (27 March 2023) with a longer follow-up (and longer exposure to capivasertib), there were some minor increases from DCO1 in the incidence of AEs reported in both treatment arms at the 27 March 2023 DCO (96.6% versus 96.9% [capivasertib + fulvestrant arm] and 82.3% versus 82.9% [placebo + fulvestrant arm], respectively), however, no new safety signal have been identified for capivasertib.

The demographics and baseline characteristics do not raise particular concerns from a safety point of view. However, it is observed that the proportion of patients with diabetes is slightly higher in the capivasertib + fulvestrant group (9.6 %) compared to the placebo + fulvestrant group (5.7%). Patients from 18 years old could be enrolled, including elderly without upper age boundary. The CAPItello-291 study was conducted in 19 countries. Among the 708 subject enrolled (capivasertib + fulvestrant and placebo + fulvestrant), 395 come from United States, Canada, Australia and Europe (among them 296 from Europe). Thus, there is no concern on the generalisation of the safety results to the European population.

The proportion of subjects who have experienced at least 1 AE is high in both groups, with 96.6% (n=343) in the capivasertib + fulvestrant group, and 82.3% (n=288) in the placebo + fulvestrant group.

Overall, higher frequencies of adverse events in any of the category were observed for capivasertib + fulvestrant compared to placebo + fulvestrant, which is expected in a study with a targeted agent added to an endocrine therapy.

Overall, the AEs commonly reported in the pivotal study are consistent with the safety profile of capivasertib from the early phase study and its mechanism of action. The safety profile of fulvestrant monotherapy is well known and AEs reported in CAPItello-291 study were consistent with this.

While the incidence of commonly reported AEs was generally higher in the FTIH Study Pool than in CAPItello-291, an exception was observed for diarrhoea (AE PT reported in 72.4% of patients in CAPItello-291 versus 65.3% of patients in the FTIH Study Pool). A possible reason for the difference in reporting rates of diarrhoea is the enhanced data collection that was in place for diarrhoea in the CAPItello-291 study. Despite the increased reporting rate of diarrhoea in CAPItello-291, the characteristics of diarrhoea AEs were similar to those reported in the FTIH Study Pool.

Although the majority of patients in the CAPItello 291 study had AEs with a maximum reported grade of 1 or 2, there were many more patients having AE of CTCAE grade 3 or higher in the capivasertib + fulvestrant arm (42.8%) than in placebo + fulvestrant arm (15.7%). There were almost 6 times more patients with AE of CTCAE grade 3 or higher, possibly related to capivasertib/placebo, in the capivasertib + fulvestrant arm (30.7%) compared to placebo + fulvestrant arm (5.4%).

Adverse events of special interest included hyperglycaemia, diarrhoea (non-infectious), rash, QT prolongation, infective pneumonia, stomatitis and urinary tract infection.

Hyperglycaemia is an expected adverse reaction of AKT inhibition.

Overall, the lower incidence of hyperglycaemia reported in the pivotal CAPItello-291 study compared to other safety pools might be explained by a more careful selection of the patient population enrolled (only 21 patient had HbA1C ≥6.5%), slightly lower dose (400 mg) used in the pivotal study and the fact that due to an intermittent schedule (four days on and three days off), a glucose homeostasis temporary recover from the AKT inhibition. In addition, education and recommendations within the protocol were provided to help identify and manage hyperglycaemia early. In section 8.4.3.5 of the CAPItello-291 CSP, there was an instruction that for all grades of hyperglycaemia, patients should receive education on lifestyle changes (i.e., a diabetic diet) and to consider starting home glucose monitoring (i.e. fasting self-blood glucose monitoring once daily).

Nevertheless, the risk of hyperglycaemia is still 4 times higher than in patients on fulvestrant monotherapy. The incidence of hyperglycaemia is expected to be much higher in the clinical setting, especially considering that the applicant proposed no restrictions on use of capivasertib in patients with diabetes mellitus type 1 or 2, The SmPC adequately reflects this lack of efficacy and safety data with capivasertib in patients with Type 1 and Type 2 diabetes requiring insulin (as these were excluded from the pivotal study). However, the lack of information on efficacy and safety in these patients remains a concern addressed in post-authorisation measures. Safety in patients with type 1 and type 2 diabetes (requiring insulin treatment or HbA1c ≥ 8.0%) is also reflected as missing information in the RMP.

Hyperglycaemia was more frequently reported in patients with a baseline HbA1C ≥ 6.5% (28.6% of patients) than those with a baseline HbA1C < 6.5% (15.4%). Severe hyperglycaemia, associated with ketoacidosis, occurred in patients treated with capivasertib. Patients with a history of diabetes mellitus may require intensified antidiabetic treatment and should be closely monitored. Consultation with a diabetologist or a healthcare professional experienced in the treatment of hyperglycaemia is recommended for patients with diabetes. This information has been added to the warning of hyperglycaemia in section 4.4 of the SmPC.

Furthermore, information has been added that before initiating treatment, patients should be informed about the potential of capivasertib to cause hyperglycaemia and to immediately contact their healthcare professional if hyperglycaemia symptoms (e.g. excessive thirst, urinating more often than usual or greater amount of urine than usual, or increased appetite with weight loss) occur. Patients should be tested for fasting blood glucose (FG) levels and HbA1C prior to treatment with capivasertib and at regular intervals during treatment.

A table with the schedule of fasting glucose monitoring and HbA1c in all patients treated with Truqap and in patients with diabetes treated with Truqap has been added as follows:

Table 78 Schedule of fasting glucose monitoring and HbA1c in all patients treated with Truqap and in patients with diabetes treated with Truqap

<table>
<tr><th></th><th>Recommended schedule for the monitoring of fasting glucose and HbA1c levels in all patients treated with TRUQAP</th><th>Recommended schedule of monitoring of fasting glucose and HbA1c levels in patients with diabetes treated with TRUQAP[1]</th></tr>
<tr><td>At screening, before initiating treatment with TRUQAP</td><td colspan="2">Test for fasting blood glucose (FG) levels, HbA1c, and optimise the patient's level of blood glucose (see Table 3).</td></tr>
<tr><td>After initiating treatment with TRUQAP</td><td colspan="2">Monitor fasting glucose at weeks 1, 2, 4, 6 and 8 after treatment start and monthly thereafter.</td></tr>
<tr><td rowspan="2"></td><td>Monitor/self-monitor fasting glucose regularly, more frequently in the first 4 weeks and especially within the first 2 weeks of treatment, according to the instructions of a healthcare professional*.</td><td>Monitor/self-monitor fasting glucose daily for the first 2 weeks of treatment. Then continue to monitor fasting glucose as frequently as needed to manage hyperglycaemia according to the instructions of a healthcare professional*.</td></tr>
<tr><td colspan="2">HbA1c should be monitored every 3 months.</td></tr>
<tr><td>If hyperglycaemia develops after initiating treatment with TRUQAP</td><td colspan="2">Monitor fasting glucose as clinically indicated (at least twice weekly, i.e. on days on and off capivasertib treatment) until FG decreases to baseline levels.
Counselling of patients on lifestyle changes is recommended.
Consultation with a healthcare practitioner with expertise in the treatment of hyperglycaemia should be considered.
Based on the severity of hyperglycaemia, TRUQAP dosing may be interrupted, reduced, or permanently discontinued (see section 4.2, Table 3).</td></tr>
<tr><td></td><td colspan="2">During treatment with anti-diabetic medication, FG should be monitored for at least once a week for 2 months, followed by once every 2 weeks or as clinically indicated.</td></tr>
<tr><td colspan="3">* All glucose monitoring should be performed at the physician's discretion as clinically indicated.
[1] More frequent FG testing is required in patients with medical history of diabetes mellitus, in patients without prior history of diabetes mellitus and showing FG of > ULN 160 mg/dL (> ULN 8.9 mmol/L) during treatment, in patient with concomitant use of corticosteroids, or in those with intercurrent infections, or other conditions which may require intensified glycaemia management to prevent worsening of impaired glucose metabolism and potential complications, namely diabetic ketoacidosis. Monitoring of HbA1C, ketones (preferably in blood) and other metabolic parameters (as indicated), in addition to FG, is recommended in these patients.</td></tr>
</table>

Additionally, at the data cut-off, the hyperglycaemia event was not recovered in 28 of the 60 patients. This is particularly of concern for patients without a history of diabetes and raises the question of a secondary risk to develop diabetes following treatment with capivasertib. This is important given the long life-expectancy of the patient population. The CSP of the study is not prescriptive on the definition of recovery, and this is thus a limitation of the interpretation of the data. Furthermore, regarding other risk factors than history of diabetes that could impact the risk of hyperglycaemia , two subpopulations were identified where a higher incidence of hyperglycaemia was found: in function of BMI and of age. However, this is also mitigated by the fact that the proportion of patients with a medical history of diabetes mellitus was higher in the BMI ≥ 30 kg/m2 group (4/66 [6.1%] patients) compared with the BMI < 30 kg/m2 group (6/285 [2.1%] patients). The difference, which remains limited, could be therefore partly explained by the history of diabetes. Although the data suggest a higher risk in elderly, the difference remains limited. Hyperglycaemia will be followed in the RMP, and relevant information and recommendations have been included in the SmPC (sections 4.2, 4.4 and 4.8).

Additional data on safety and efficacy in patients with diabetes are needed to give evidence-based recommendations to prescribers, when patients with concomitant diabetes mellitus should be part of the target population. Section 4.4 of the SmPC states that these patients can receive capivasertib, but should be closely monitored and may require intensified diabetic treatment. Fasting blood glucose and HbA1C

should be assessed and blood glucose optimised prior to treatment. It is considered that optimisation of glucose status should be a prerequisite for the start of capivasertib therapy. Furthermore, the applicant confirms that patients with diabetes mellitus type 1 or diabetes mellitus type 2 requiring long-term insulin treatment will be eligible for future studies of capivasertib, such that data can be anticipated in future on the use of capivasertib in this group of patients. The capivasertib Phase IIIb programme consists of studies CAPItana, CAPItrue and CAPIcorn and for all these studies the updated exclusion criteria include: Clinically significant abnormalities of glucose metabolism defined as HbA1c ≥8.0% (63.9 mmol/mol) at screening. Collectively these three studies will enrol ~600 patients. The applicant is recommended to plan subgroup analyses on efficacy (ORR, PFS, OS) in diabetic patients in the individual studies and in the combined analyses. Results of such studies (CAPItana, CAPItrue and CAPIcorn) should be submitted once available (REC). However, it is predicted that insulin dependent diabetic patients will represent only a small percentage of the recruited population. The applicant was therefore requested to investigate the feasibility of conducting a non-interventional study to jointly investigate the efficacy and safety of capivasertib in patients with type 1 or type 2 diabetes, including those with insulin-dependent diabetes, with sufficient patients to characterise efficacy in patients with diabetes mellitus type 1 or diabetes mellitus type 2 requiring insulin treatment. Overall, the applicant's approach and a proposal to conduct a non-interventional PASS (category 3 study in the RMP) is considered acceptable. In order to provide the prescribers with the most recent recommendations for precautionary measures, monitoring and handling of capivasertib-induced hyperglycaemia for all patients (including patients with diabetes or risk factors), sections 4.2 and 4.4, subsection Hyperglycaemia have been updated. "Safety in patients with type 1 or type 2 diabetes (requiring insulin treatment, or HbA1c ≥ 8.0%)" is reflected as missing information in the RMP.

Successful management of hyperglycaemia induced by capivasertib is of the utmost importance. In the setting of a clinical trial, hyperglycaemia may be considered manageable; however, in the clinical setting, hyperglycaemia and related events may be fatal, as they may not be diagnosed on time. "Acute complications of hyperglycaemia" has been added as an important potential risk in the RMP.

The incidence of diarrhoea AESIs was 3.5x higher in the capivasertib + fulvestrant arm. Almost all the cases of Grade 3 occurred in the capivasertib + fulvestrant arm (n=33, 9.3% ; vs. n=1, 0.3% in the placebo + fulvestrant arm). SAEs were reported in 1.7%, and diarrhoea lead to discontinuation in 2% of the patients in the capivasertib + fulvestrant arm. The events typically occurred during the three first weeks of treatments. The management of these events is particularly of concern considering the potential related risk of dehydration, electrolyte disturbances including hypokalaemia and thus a potential risk of cardiac arrhythmia, and acute kidney injury (i.e. Secondary risks of diarrhoea). In the majority of patient, diarrhoea appeared to be manageable with medication and/or dose interruptions/adjustments. This information has been added to the warning in section 4.4 of the SmPC, advising that based on the severity of the diarrhoea, Truqap dosing may be interrupted, reduced, or permanently discontinued and advising patients to start anti-diarrhoeal treatment at the first sign of diarrhoea and to increase oral fluids if diarrhoea symptoms occur during treatment. Maintenance of normovolaemia and electrolyte balance is required in patients with diarrhoea to avoid complications related to hypovolemia and low electrolyte levels. The applicant agreed to closely monitor "Acute complications of diarrhoea" and report it in future PSURs.

Skin rash is a class-effect observed with PI3K/AKT/PTEN signalling pathway inhibitors. The incidence of rash AESIs was higher in the capivasertib + fulvestrant arm (38.0% vs 7.1%), and occurred with greater severity. Localisation or body surface area of the rash was reported for 13 of the 43 patients with Grade 3 rash (grouped term). Overall, the localisation varied among the patients reported so that no conclusion can be drawn.

Grade ≥ 3 skin ADRs (includes Grade ≥ 3 rash AESI, PTs of erythema, rash erythematous, erythema multiforme, drug eruption, and dermatitis exfoliative generalised) represent one of the key risks of

capivasertib treatment and were reported in 53 patients (14.9%) in the CAPitello-291. Onset was typically during the second week of treatment. Capivasertib was interrupted in 39/53 patients (73.6%), and dose reduced in 17/53 patients (32.1%), with total of 13/53 patients (24.5%) discontinuing treatment due to CTCAE ≥ Grade 3 skin ADRs. The most patients recovered or were recovering at the DCO. A warning in section 4.4 of the SmPC has been added informing that skin drug reactions, including erythema multiforme and dermatitis exfoliative generalised, were reported in patients receiving capivasertib and that patients should be monitored for signs and symptoms of rash or dermatitis and based on severity of skin drug reactions, the dosing may be interrupted, reduced, or permanently discontinued. Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management. Additional information describing rash has also been added in section 4.8 under the ADR table. "Severe cutaneous adverse reactions" will be closely monitored and discussed in PSURs.

One SAE of anaphylactic reaction (Grade 3) was reported. The event was considered by the Investigator as possibly related to capivasertib and fulvestrant, and the patient experienced previously a Grade 3 rash maculo-papular possibly related to capivasertib. Based on the additional information provided, it cannot be excluded that rash was a sign of sensitisation. However, considering that the patient has also received concomitantly fulvestrant, and that there is no additional cases, it appears difficult to conclude and provide additional guidance. Furthermore, the risk of hypersensitivity and rash are both mentioned in sections 4.4 (rash and other skin drug reactions) and 4.8 (rash and hypersensitivity) of the SmPC.

In most patients, rash was managed with topical corticosteroids or antihistamine treatment, however in a third of the patients requiring treatment, systemic corticosteroids were used. Systemic corticosteroids, among other, are known to induce hyperglycaemia. The applicant provided an additional analysis of the data from the CAPItello 291 and discussed the potential risk of the concomitant use of systemic corticosteroids and capivasertib. Overall, a slight trend towards higher rate of hyperglycaemia events was reported in patients that used systemic corticosteroids, and a higher rate of patients receiving systemic corticosteroids required treatment for hyperglycaemia. Although caution should be exercised when interpreting these data due to the small number of patients in the group who received concomitant systemic corticosteroids (N = 40), it does not diminish the fact that concomitant use of systemic corticosteroids and capivasertib may pose an additional risk for the patients and this has been reflected in the proposed SmPC, under section 4.4, subsection hyperglycaemia.

In addition, the applicant has clarified that the primary prophylaxis against drug-induced rash was not mandated nor recommended in the protocol for the CAPItello-291 study but was not restricted, whereas secondary prophylaxis by continuing topical steroids and/or non-sedating oral antihistamines was permitted. Considerations for secondary prophylaxis with antihistamines are included in Section 4.2.

QT prolongation was identified as being an AESI in the CAPItello-291 study based on non-clinical data. The AEs defined by the AESI category of QT prolongation were reported in 11 patients in the capivasertib + fulvestrant arm and included electrocardiogram QT prolonged, syncope, seizure, and ventricular arrhythmia. Although low in incidence, most were reported as AEs of CTCAE Grade 3 and included syncope (6 patients, 1.7%), and electrocardiogram QT prolonged and seizure (each in 1 patient, 0.3%). The events typically occurred within the initial few weeks of treatment. In 2 patients, the events (both electrocardiogram QT prolonged) led to dose interruptions. None led to discontinuation of treatment. Most had recovered or were recovering at the time of DCO1. Electrocardiogram QT prolonged was reported in 3 of the 11 patients. In all 3 patients additional risk factors that might have increased the risk of a long QT interval were identified (hypokalaemia due to diarrhoea; co-administration of indapamide; low calcium levels). However, in all of these patients, ECG at any visit showed QTcF interval within the normal range.

Of note, most of ECGs were taken in a days off capivasertib treatment which might have influenced the characterisation of ECGs.

The applicant provided a listing of the QT prolongations (Narrow Torsade de pointes/QT prolongation MedDRA SMQ) that were observed in all applicant-sponsored studies. Overall, QT prolongations were reported in 29 patients, mostly were not serious and majority were grade 1 in severity. A case of a ventricular tachycardia (serious) was reported in one patient that received capivasertib 480 mg BID (4 on 3o ff), and drug was permanently discontinued.

The applicant has also informed that more extensive monitoring of ECGs is being conducted in the Capitello-290 study and the ECGs were recorded at the time of steady state Cmax. Therefore, it is expected that further characterisation of the ECGs will be possible and the applicant is recommended to address the issue once data from the CAPItello-290 study are available (**REC**).

The applicant has provided tables with all AEs in the Cardiac arrhythmias HLGT reported in the CAPItello 291. With a total of 14 (3.9%) patients in the capivasertib + fulvestrant arm and 4 (1.1%) of patients in the placebo + fulvestrant arm that had AEs in the Cardiac arrhythmias HLGT, a slight imbalance between treatment arms is noted, mostly driven by 4 vs 1 AEs of sinus tachycardia in the capivasertib + fulvestrant vs placebo + fulvestrant arm, respectively. Furthermore, 2 AEs were classified as SAEs but they were not considered related to either of the study treatment.

As with patients with QT prolongation AESI, also Cardiac arrhythmias AEs have shown a trend for being reported more frequently in the capivasertib + fulvestrant arm than in the control arm. Not excluding the possibility of chance finding, the contribution of capivasertib also cannot be completely ruled out. The information that cardiac arrhythmias with hypokalaemia as risk factor have been reported in patients receiving capivasertib plus fulvestrant in clinical trials is therefore included in section 4.4 of the SmPC. Furthermore, a warning has been added to Section 4.4 of the SmPC describing that the CAPItello 291 study excluded patients with medical history of clinically significant cardiac disease including QTcF >470 msec, any factors that increased the risk of QTc prolongation or risk of arrhythmic events or risk of cardiac function impairment and that this should be considered if prescribed in these patients. "Use in patients with clinically important abnormalities in cardiac rhythm (e.g., QT prolongation)" has also been added as missing information in the RMP.

Regarding urinary tract infection, the proportion of patients experiencing the event was higher in the capivasertib + fulvestrant arm, with 14.1% (n=50) compared to the placebo + fulvestrant arm with 6.9% (=24), while all the cases of Grade 3 occurred in the capivasertib + fulvestrant arm (n=7, 2.0%). The event is included in the list of the adverse drug reactions in section 4.8 of the SmPC and no warning in the SmPC has been included at this stage.

In the pivotal study, there was a slightly higher proportion of patients with renal AEs of potential interest of all grades in the capivasertib + fulvestrant arm compared to the placebo + fulvestrant arm and the incidence of blood creatinine increased AEs was higher in the capivasertib + fulvestrant arm (4.5% vs 0.3%). Higher rate of blood creatinine increase in capivasertib + fulvestrant arm is probably due to decreased tubular secretion of creatinine, since capivasertib is known to inhibit the renal transporters OCT2, MATE1, and MATE2K in vitro. Further, 5 cases of acute kidney injury during or within 7 days after a diarrhoea AE were reported, indicating that diarrhoea may not be adequately manageable in some patients, and also considering two patients discontinued capivasertib treatment due to acute kidney injury. AKI is currently listed as an ADR in section 4.8 and the risk of AKI in patients with drug-induced diarrhoea is reflected in section 4.4.

In non-clinical studies, the liver had been identified as tissues affected by capivasertib. Overall, in the capivasertib pivotal study no signal of increased hepatotoxicity has been so far identified. Liver function-related findings raised overall no concerns.

Serious AEs with fatal outcome were reported in 4 patients in the capivasertib + fulvestrant arm, vs. 1 in the placebo + fulvestrant arm. None were related to the study treatment. As requested, the relatedness of the AEs with fatal outcomes was further discussed, but overall, at this stage, it does not lead to draw further conclusion on the safety profile of capivasertib.

It may be assumed that better handling the AEs caused by treatment with capivasertib probably could have prevented some of the deaths in capivasertib + fulvestrant arm, which is why adequate measures for management of capivasertib toxicity and patient education are essential for the clinical setting.

Serious AEs were also more frequent in the capivasertib + fulvestrant arm. SAEs considered by the investigator as possibly related to capivasertib only and reported in more than 1 patient in the capivasertib + fulvestrant arm were diarrhoea (6 patients, 1.7%), rash maculo-papular (5 patients, 1.4%), acute kidney injury, hyperglycaemia, and vomiting (each in 3 patients, 0.8%), and asthenia (2 patients, 0.6%).

In both the FTIH Study Pool and in the Monotherapy Pool, SAEs were reported in a higher proportion of patients than in the pivotal trial (32.0% vs 43.0% vs 16.1%, respectively). For the Monotherapy pool, this may be explained with a higher dose of capivasertib given to this patient population. Higher incidence of SAEs reported in FTIH Study Pool might be explained with the fact that more heavily pre-treated patients were enrolled in the study (indicating that patients in the FTIH study had more advanced disease). Furthermore, since toxicity management guidelines were revised over time and were more prescriptive for the CAPItello-291 study, this might be the reason why in the CAPItello-291 study the AEs were managed earlier and more aggressively and were less likely to reach the level of an SAE.

In the CAPItello 291 study, haematological abnormalities were predominantly Grade 1 or 2; Grade 3 abnormalities were comparable between the treatment arms, except for Grade 3 decreases in lymphocytes and haemoglobin which were reported more frequently in the capivasertib + fulvestrant arm. Consistent with the haemoglobin data, there were more AEs of anaemia reported in the capivasertib + fulvestrant arm (10.4% vs 4.9%).

There were 15 (4.2%) patients in the capivasertib + fulvestrant arm and 2 (0.6%) patients in the placebo + fulvestrant arm with AEs of hypokalaemia during the study. Hypokalaemia AEs were CTCAE Grade 3 in 7 (2.0%) patients and CTCAE Grade 4 in one (0.3%) patient in the capivasertib + fulvestrant arm.

The patient reported outcomes focusing on safety/toxicity indicate overall an unfavourable impact on treatment-related symptoms, including diarrhoea, rash and mouth or throat sores when capivasertib is added to fulvestrant. The proportion of patients reporting higher severity, interference, frequency or presence of the assessed PRO-CTCAE items was higher in the capivasertib + fulvestrant arm.

Rash and mouth or throat sores symptoms recorded by the patients on the PRO-CTCAE tended to peak in frequency, intensity, severity, and/or impact on daily life in the early cycles of treatment in both treatment arms. Diarrhoea, on the other hand, retained its frequency and, in a certain number of patients, severity in the later cycles as well.

With regards to effect of age, the overall incidence of AEs, SAEs, and AESIs in the capivasertib + fulvestrant arm of CAPItello-291 was similar across all 3 age groups presented. The incidence of CTCAE Grade 3 or higher AEs was higher in the 65 to 74 years (58.2%) and ≥ 75 years (54.2%) age groups than in the < 65 years age group (35.8%). Owing to the imbalance in the number patients per age group, differences between groups should be interpreted with caution, and limited conclusions can be drawn for the ≥ 75 years age group, which comprised only 6.8% of patients in the capivasertib + fulvestrant arm of CAPItello-291.

No conclusions can be drawn on effect of sex due to the small number of male patients in capivasertib clinical programme.

Although overall incidence of AEs in the capivasertib + fulvestrant arm of CAPItello-291 was generally similar across the weight subgroups, considering the incidences of SAEs and AEs leading to dose reduction were higher in the baseline weight < 50 kg group, it could be that 400 mg may not be an optimal dose in the baseline weight < 50 kg group (see discussion on clinical pharmacology).

Capivasertib's safety profile was generally consistent between altered, confirmed non-altered subgroup SAS and overall safety analysis set. AEs reported in the altered/ confirmed non-altered subgroup SAS reflected those of the overall SAS, with no notable differences.

The frequency of overdoses was highest in Cycle 1 and seemed to decrease thereafter. Overall, the majority of cases occurred on non-dosing days. This indicates that overdose occurred mainly due to the intermittent capivasertib application, probably as patients were not accustomed of taking medications in this way. One of these patients had an overdose associated with an AE (SAE of diarrhoea, diabetic metabolic decompensation and renal failure). This patient was exposed to capivasertib for 14 consecutive days during cycle 1 week 1 and cycle 1 week 2. The information that the higher than the indicated dosing of capivasertib can increase the risk of capivasertib adverse reactions, including diarrhoea has been added in section 4.9. of the proposed SmPC.

Although the incidence of AEs leading to discontinuation of capivasertib was higher in the capivasertib + fulvestrant arm (13.0% vs 2.3% in the placebo + fulvestrant arm), it is considered acceptable for this patient population. The most frequent AEs leading to discontinuation in the capivasertib arm were rash/rash maculo-papular (4.5%), vomiting and diarrhoea (2.0% each), and pyrexia (1.1%). Most of the discontinuations of capivasertib (regardless of fulvestrant discontinuation) occurred during the early cycles of treatment. Only one patient discontinued capivasertib treatment due to hyperglycaemia. Of note, AEs leading to discontinuation were more frequent in confirmed non-altered group (16.9%) than in the confirmed altered group (10.3%).

Adverse events requiring dose modification were also much more frequent in capivasertib + fulvestrant arm.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

2.6.10. Conclusions on the clinical safety

The safety data from the CAPItello-291 study, supported by pooled safety data from relevant studies with capivasertib are reasonably sufficient to characterise the safety profile of capivasertib administrated in combination with fulvestrant and overall indicate an acceptable tolerability profile, despite the fact that the combination of capivasertib plus fulvestrant was more toxic than fulvestrant monotherapy.

In the pivotal CAPItello 291- study no unexpected toxicities occurred. The rates of AEs across categories were higher in the capivasertib + fulvestrant arm than in the placebo + fulvestrant arm, however, this is expected considering a targeted therapy added to an endocrine therapy. Most adverse events appear to be manageable with standard care measures and dose modifications.

The key risks identified for capivasertib are hyperglycaemia and CTCAE ≥ Grade 3 skin ADRs. Diarrhoea is in general manageable in the majority of patients. Nevertheless, the risk of acute complications of diarrhoea is of concern in the clinical setting.

The lack of efficacy and safety data for capivasertib in patients with Type 1 and Type 2 diabetes requiring insulin (as these were excluded from the pivotal study) is adequately reflected in the SmPC. The applicant confirmed that patients with diabetes mellitus type 1 or diabetes mellitus type 2 requiring long-term insulin treatment will be eligible for future studies of capivasertib, such that data can be anticipated in

the future on the use of capivasertib in this group of patients. In particular, the capivasertib Phase IIIb programme consists of studies CAPItana, CAPItrue and CAPIcorn and for all these studies the updated exclusion criteria include: Clinically significant abnormalities of glucose metabolism defined as HbA1c ≥8.0% (63.9 mmol/mol) at screening. Collectively these three studies will enrol ~600 patients, however, it is predicted that insulin dependent diabetic patients will represent only a small percentage of the recruited population. The applicant agreed to investigate the feasibility of conducting a non-interventional PASS to investigate the safety as well as the efficacy of capivasertib in patients with type 1 or type 2 diabetes, including those with insulin-dependent diabetes, with sufficient patients to characterise efficacy in patients with diabetes mellitus type 1 or diabetes mellitus type 2 requiring insulin treatment. Overall, the applicant's approach and proposal to conduct a non-interventional PASS is considered acceptable.

Furthermore, the relevant data from the CAPItello-290 study for the further characterisation of capivasertib contribution to QT prolongation will be provided when available (REC).

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 79 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Complications of hyperglycaemia
Missing information	Safety in patients with type 1 and type 2 diabetes (requiring insulin treatment, or HbA1c ≥ 8.0%) Use in patients with clinically important abnormalities in cardiac rhythm (e.g., QT prolongation)

2.7.2. Pharmacovigilance plan

Table 80 On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
A database study of the safety and effectiveness of TRUQAP (capivasertib) + fulvestrant in patients with advanced breast cancer and type 1 or type 2 diabetes Planned	To assess the effectiveness and safety of TRUQAP + fulvestrant in patients with advanced breast cancer and diabetes (type 1 or type 2; insulin- or non-insulin-dependent) who have received prior endocrine treatment	Safety in patients with type 1 and type 2 diabetes (requiring insulin treatment, or HbA1c ≥ 8.0%)	Submission of feasibility report	July 2024
			Protocol submission	October 2024
			Interim report completion	Q3 2027
			Final study report completion	Q3 2030

2.7.3. Risk minimisation measures

Table 81 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risk		
Complications of hyperglycaemia	**Routine risk minimisation measures:** • SmPC Section 4.4 • PL Section 2 • Prescription-only medicine. **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up questionnaire. **Additional pharmacovigilance activities:** • None
Missing Information		
Safety in patients with type 1 and type 2 diabetes (requiring insulin treatment, or HbA1c ≥ 8.0%)	**Routine risk minimisation measures:** • SmPC Section 4.4 • PL Section 2 **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • A database study of the safety and effectiveness of TRUQAP (capivasertib) + fulvestrant in patients with advanced breast cancer and type 1 or type 2 diabetes
Use in patients with clinically important abnormalities in cardiac rhythm (e.g. QT prolongation)	None.	None.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD).

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Truqap (capivasertib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The recommended indication reflecting the data evaluated is:

"*TRUQAP is indicated in combination with fulvestrant for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2negative locally advanced or metastatic breast cancer with one or more*

PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine-based regimen (see section 5.1).

In pre- or perimenopausal women, TRUQAP plus fulvestrant should be combined with a luteinising hormone releasing hormone (LHRH) agonist.

For men, administration of a LHRH agonist according to current clinical practice standards should be considered. "

3.1.2. Available therapies and unmet medical need

For metastatic breast cancer the 5-year survival rate is in the range of 38% (Allemani et al, Lancet, 2018). Metastatic breast cancer is the leading cause of death from all cancers in women, accounting for ~3.6% of all deaths in women and 1.8% of all deaths in Europe in 2015 (Dafni et al, Breast Care, 2019).

The combination of endocrine therapy with a CDK4/6 inhibitor (CDK4/6i) is currently considered the standard of care first-line treatment in the majority of patients with oestrogen receptor-positive (ER+), HER2-negative locally advanced or metastatic breast cancer, with improved PFS and OS seen in several trials. For the choice of next-line treatment, disease burden, duration of response to previous endocrine therapy, previously used medicinal agents, treatment availability etc. need to be considered. According to ESMO Guidelines, evidence-based available options for second-line therapy are in principle fulvestrant-alpelisib (for *PIK3CA* mutated tumours), exemestane-everolimus, fulvestrant monotherapy, PARP inhibitors (for tumours harbouring genomic *BRCA* mutations), trastuzumab deruxtecan (for HER2-low tumours), elacestrant (for ESR1 mutated tumours), aromatase inhibitors, and chemotherapy. After progression on CDK4/6i the optimal sequence is uncertain due to limited data in CDK 4/6i-pretreated patients for several of these options (e.g. alpelisib).

Substances targeting the same signalling pathway as capivasertib are alpelisib and everolimus. In study SOLAR-1, alpelisib was investigated in postmenopausal women in 2 cohorts, *PIK3CA* mutated tumours and non-mutated tumours. Results for PFS were reported with an HR of 0.65 (95%CI 0.50-0.85) for *PIK3CA* mutated tumours, whereas no PFS benefit was observed in patients whose tumours did not have a PIK3CA tissue mutation.

Premenopausal women should receive ovarian suppression/ablation when treated with aromatase inhibitors or SERDs.

3.1.3. Main clinical studies

Study D3615C00001 (CAPItello-291) (NCT04305496) is an ongoing Phase III, double-blind, placebo-controlled, parallel-group, randomised, multicentre study to investigate the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant in 708 patients with ER+, HER2- locally advanced or metastatic breast cancer following disease recurrence or progression on or after aromatase inhibitor therapy. Patients may have received previously CDK 4/6i, up to 2 lines of endocrine treatment and 1 line of chemotherapy. Randomisation (1:1) was stratified by presence of liver metastases, prior use of CDK4/6 inhibitors and geographic location.

The study was planned to show a statistically significant difference between capivasertib + fulvestrant versus placebo + fulvestrant in PFS in the *Overall population* and the *PIK3CA/AKT1/PTEN-altered Population* (dual primary endpoints) and OS (key secondary endpoint) in both populations. For the complimentary non-altered population the same endpoints were exploratory analysed.

Supportive study FAKTION (NCT01992952) is a phase 1b/2 study with a randomised (1:1), double-blind, placebo-controlled phase 2 part comparing capivasertib + fulvestrant versus placebo + fulvestrant in

140 post-menopausal women with locally advanced or metastatic ER+/HER2- breast cancer following recurrence or progression on or after aromatase inhibitor therapy, no previous CDK4/6 inhibitor. The phase 2 part of the study was published twice: first the primary analysis by Jones et al in 2020 and the updated clinical study and expanded biomarker data by Howell et al. in 2022. Only the publications were provided.

The studied dosing regimen was capivasertib 800 mg daily (400 mg BD with or without food) for 4 days followed by 3 days off treatment, fulvestrant 500 mg was administered on Days 1, 15, and 29, and once monthly thereafter. Study treatment was continued until disease progression or unacceptable toxicity. In pre/perimenopausal women, capivasertib plus fulvestrant was to be combined with a luteinizing hormone releasing hormone (LHRH) agonist.

3.2. Favourable effects

The presented data are from the primary analysis for superiority of the primary efficacy endpoint of progression free survival (PFS) assessed by investigator in the PIK3CA/AKT1/PTEN altered population at the data cut-off (DCO) date of 15 August 2022.

Primary endpoint: PFS by investigator in the PIK3CA/AKT1/PTEN altered population (n=289): Median PFS was 7.3 months (95%CI: 5.5, 9.0) in the capivasertib+fulvestrant arm versus 3.1 months (95%CI: 2.0, 3.7) in the placebo+fulvestrant arm, the hazard ratio was 0.50 (95% CI: 0.38 – 0.65; $p < 0.001$).

Key secondary endpoint: Overall survival (OS) in the PIK3CA/AKT1/PTEN altered population: HR of 0.69 (95% CI 0.45, 1.05)

The early analysis on OS at the time of the primary PFS analysis did not suggest a detrimental effect on survival of treatment with capivasertib + fulvestrant compared with placebo + fulvestrant. Kaplan-Meier plots appear to diverge early.

Sensitivity analysis of PFS by BICR in the PIK3CA/AKT1/PTEN altered population (HR: 0.51; 95% CI: 0.38 – 0.68; $p < 0.001$) was consistent with the primary PFS analyses.

Subgroup analyses of PFS: an homogenous effect in most subgroups (by prior chemotherapy, by prior CDK 4/6i treatment, by metastatic site or primary/secondary endocrine resistance) was observed.

Supportive FAKTION study in postmenopausal patients reported for NGS identified pathway altered population for PFS an HR of 0.35 (95% CI 0.20, 0.63) and for OS an HR of 0.43 (95% CI 0.24, 0.78) (Howell et al. 2022).

3.3. Uncertainties and limitations about favourable effects

CAPITELLO-291 OS data are immature (28%) in the *PIK3CA/AKT1/PTEN altered population*, and the applicant will submit further OS analyses (REC)**.**

There remains a level of uncertainty regarding the benefit in pre/perimenopausal patients due to the small size of this subgroup in the CAPITELLO-291 study. The effect size for PFS was smaller and the confidence intervals wide. For this subgroup more unfavourable baseline characteristics were recorded which may have contributed. However further studies investigating capivasertib in combination with other medicinal products (CAPItello-292 and CAPItello-290) will provide further efficacy data for capivasertib in women in premenopausal state and the results of such studies should be submitted when available (REC).

It is uncertain to what extent the efficacy data in the rather 'fit' and non-diabetic study population from CAPITELLO-291 (with the exclusion of patients with insulin dependent diabetes mellitus or high HbA1C)

can be extrapolated to the target population with diabetes and on antidiabetic medication. Insulin can act as mitogen activating MAPK/ERK and PI3K/AKT signalling, this systemic feedback may impair treatment efficacy with capivasertib. A post-authorisation study (included as a category 3 in the RMP) is planned to address the safety as well as efficacy in patients with diabetes mellitus type 1 or diabetes mellitus type 2 requiring long-term insulin treatment as this is currently lacking. 3 further studies which are part of the capivasertib phase IIIb study program (approximately 600 patients to be included) will allow inclusion of patients with pre-existing diabetes and HbA1C ≤8mg/dl. Enrolment of diabetic patients and plan for subgroup analyses on efficacy (ORR, PFS, OS) in diabetic patients in the individual studies and in the combined analyses are encouraged (REC).

There remains a level of uncertainty regarding the in-vitro diagnostic used for definition of PIK3CA/AKT1/PTEN mutational status used in pivotal study CAPItello-291 (FoundationOne®CDx (F1CDx)): the justification for the definition of biomarker-positivity (i.e. PIK3CA/AKT1/PTEN alterations as specified) is following a scientific rationale mainly based on preclinical data. The exploratory clinical data from the CAPItello-291 study suggest that the definition applied may indeed be predictive. However, this is no final confirmation of clinical validity for all individual genetic alterations included.

As no clinical thresholding for the cut-point defining a tumour as biomarker positive or negative was performed, it remains unclear whether the thresholds / cut-off values applied in study CAPitello-291 were optimal or whether a higher or lower thresholds defining patients as 'PIK3CA/AKT1/PTEN alteration-positive' would lead to an even better benefit-risk ratio.

3.4. Unfavourable effects

In the CAPItello 291 study, higher frequencies (≥10%) in the capivasertib + fulvestrant arm compared to the placebo + fulvestrant arm were observed for any TEAEs (96.6% vs 82.3%), treatment-related TEAEs (63.3% vs 43.7%), any TEAEs Grade 3 or higher (42.8% vs 15.7%) and TEAEs leading to dose interruption (15.2% vs 5.2%), to dose reduction (19.7% vs 1.7%) and dose discontinuation (13.0% vs 2.3%).

The most commonly reported AEs (> 20% of patients) in the capivasertib + fulvestrant arm were: diarrhoea (72.4% in the capivasertib + fulvestrant arm vs 20.0% in the placebo + fulvestrant arm), nausea (34.6% vs 15.4%), rash (22.0% vs 4.3%), fatigue (20.8% vs 12.9%), and vomiting (20.6% vs 4.9%). Other AEs occurring more commonly in the capivasertib + fulvestrant arm (> 10% difference between treatment arms) were decreased appetite (16.6% versus 6.3%), hyperglycaemia (16.3% versus 3.7%), and rash maculo-papular (16.1% versus 3.7%).

There was a higher proportion of patients with Grade 3 AEs in the capivasertib + fulvestrant arm (39.2% compared with 12.5%) and similar numbers of patients with Grade 4 AEs in both groups (capivasertib + fulvestrant arm, 2.5%; placebo + fulvestrant arm 2.9%). The most commonly occurring AEs of CTCAE Grade 3 or higher in the capivasertib + fulvestrant arm were diarrhoea (33 patients, 9.3%), rash maculo-papular (22 patients, 6.2%), rash (19 patients, 5.4%), hyperglycaemia and hypokalaemia (8 patients, 2.3% each).

The AESIs for capivasertib include hyperglycaemia, diarrhoea (termed non-infectious diarrhoea in the CSP), rash, QT prolongation, infective pneumonia, stomatitis and UTI.

SAEs were reported in a higher proportion of patients in the capivasertib + fulvestrant arm compared to the placebo + fulvestrant arm (16.1% vs 8.0%) in the CAPItello 291 study. The most frequently reported SAEs were diarrhoea, rash maculo-papular, and vomiting.

87 patients (24.5%) in the capivasertib + fulvestrant arm and 108 patients (30.6%) in the placebo + fulvestrant arm had died, the majority of deaths classified as due to progression of disease. Overall,

eight deaths in the capivasertib + fulvestrant and six in the placebo + fulvestrant arm occurred for other reasons including AEs and none was considered by the investigator as related to study treatment.

The key risks identified with capivasertib are hyperglycaemia and CTCAE ≥ Grade 3 skin ADRs. Diarrhoea is in general considered manageable in the majority of patients. Nevertheless, the risk of acute complications of diarrhoea and hypokalaemia as a risk factor for cardiac arrhythmia is of concern in the clinical setting.

QT prolongation (identified as AESI based on non-clinical data) was reported in 11 patients in the capivasertib + fulvestrant arm and included electrocardiogram QT prolonged, syncope, seizure, and ventricular arrhythmia.

3.5. Uncertainties and limitations about unfavourable effects

The lack of safety data for capivasertib in patients with Type 1 and Type 2 diabetes requiring insulin is reflected in section 4.4 of the SmPC (as these were excluded from the pivotal study). In order to address this uncertainty, a non-interventional post authorisation safety study (category 3 study in the RMP) will be conducted to investigate the safety of capivasertib in patients with type 1 or type 2 diabetes, including those with insulin-dependent diabetes.

Successful management of hyperglycaemia induced by capivasertib is of utmost importance. In the setting of a clinical trial, hyperglycaemia may be considered manageable; however, in the clinical setting, hyperglycaemia and related events may be fatal as they may not be diagnosed on time. Therefore, sections 4.2 and 4.4 of the SmPC include detailed information on precautions and management of hyperglycaemia.

Although on the available ECG recordings of patients experiencing syncope or seizure, QT prolongation could not be seen, it is still concerning and raises questions why these have only been reported in capivasertib + fulvestrant arm and especially because the patients with clinically important abnormalities in cardiac rhythm or any factors that increase the risk of QTc prolongation or arrhythmic events were excluded from the study. Relevant data from the CAPItello-290 study should be provided for the further characterisation of capivasertib contribution to QT prolongation (REC).

3.6. Effects Table

Table 82 Effects Table for capivasertib in combination with fulvestrant in the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer following recurrence or progression on or after an endocrine based regimen – CAPItello 291 (data cut-off: 15 August 2022)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS *PIK3CA/AKT1/ PTEN altered population*	Progression-free survival	Median in months (95%CI)	7.3 (5.5, 9.0)	3.1 (2.0, 3.7)	**Strengths**: RCT, treatment blinded **Uncertainties:** biomarker test retrospectively performed time-point of assignment to population unclear	CSR

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
OS *PIK3CA/AKT1/ PTEN altered population*	Overall survival	Median in months (95%CI)	NC (NC, NC)	NC (20.3, NC)	**Strengths**: RCT, treatment blinded **Uncertainties** immature	CSR
Unfavourable Effects						
AEs	Overall incidence of adverse events	Proportion (%)	96.6	82.3		CSR
Grade 3 or higher	Incidence of adverse events of grade 3 or 4	Proportion (%)	42.8	15.7		CSR
SAEs	Incidence of serious adverse events	Proportion (%)	16.1	8.0		CSR
AEs leading to discontinuation	Incidence of discontinuations due to adverse events	Proportion (%)	13.0	2.3		CSR
Diarrhoea	Common adverse event and AESI	Proportion (%)	72.4	20.0		CSR
Rash	Common adverse event and AESI (includes rash, rash macular, rash maculo-papular, rash papular, rash pruritic)	Proportion (%)	38.0	7.1		CSR
Hyperglycaemia	Common adverse event and AESI	Proportion (%)	16.3	3.7		CSR
Grade ≥ 3 skin ADRs	includes Grade ≥ 3 rash AESI, PTs of erythema, rash erythematous, erythema multiforme, drug eruption, and dermatitis exfoliative generalised	Proportion (%)	14.9	0.3		CSR
QT Prolongation	AESI	Proportion (%)	3.1	0		CSR

Abbreviations:
Notes: See Figures

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In CAPITELLO-291, 40.8% of the overall population belonged to the PIK3CA/AKT1/PTEN altered population. In the PIK3CA/AKT1/PTEN altered population, the effect on PFS in favour of capivasertib+fulvestrant in the primary analysis is statistically significant and clinically relevant with more than doubling of the median PFS time i.e. 4.2 months. PFS sensitivity and subgroup analyses support the robustness of this favourable effect. Importantly for such heterogeneous target population, the effect on PFS was homogenous over most subgroups, thus it was independent of prior CDK 4/6i treatment, prior chemotherapy in the metastatic setting or site of metastatic disease.

Early analyses on OS did not suggest a detrimental effect on survival and further analyses of OS are planned. Results from other secondary endpoints (ORR, PFS2) are supportive which is reassuring.

Published results from the supportive FAKTION study including mature OS data underline a clinically relevant effect on PFS and even reported an OS benefit in favour of capivasertib+fulvestrant in the biomarker positive population. This is independent of the detailed definition for PIK3CA/AKT1/PTEN alteration and is most pronounced in the subsequent biomarker analysis for which the same biomarker definitions (NGS-identified) are used as in CAPitello-291.

The key risks identified for capivasertib are diarrhoea, hyperglycaemia and CTCAE ≥ Grade 3 skin ADRs. When interpreting the safety results it has to be kept in mind that patients with frequent and relevant concomitant diseases (diabetes, cardiac diseases) or concomitant medication with influence on QT interval were excluded from the pivotal study.

The risk of hyperglycaemia is considered highly important as it is four times higher than in patients on fulvestrant monotherapy. The incidence of hyperglycaemia is expected to be even much higher in the clinical setting, especially considering that the applicant proposes no restrictions on use of capivasertib in patients with diabetes mellitus type 1 or 2. In the patients with a history of diabetes (not requiring insulin at baseline) which were included in the pivotal study, the safety data that was reported indicate a worse safety profile in comparison to patients without a history of diabetes.

A non-interventional post authorisation safety study (category 3 study in the RMP) will be conducted to investigate the safety of capivasertib in patients with type 1 or type 2 diabetes, including those with insulin-dependent diabetes. "Safety in patients with type 1 or type 2 diabetes (requiring insulin treatment, or HbA1c ≥ 8.0%)" is reflected as missing information in the RMP.

Diarrhoea is reported as manageable in general in the clinical trial setting. However, it is considered important for the patient population as it was reported in the majority of patients and with approximately 9% CTCAE ≥ Grade 3. The risk of acute complications of diarrhoea, e.g. dehydration, and hypokalaemia as a risk factor for cardiac arrhythmia are of concern in the clinical setting of a target population that is likely to present with more concomitant diseases than the clinical study population.

The risk of QT prolongation is considered relevant and important. QT prolongation was identified as an AESI based on non-clinical data. QT prolongation was reported in 11/430 patients under capivasertib + fulvestrant treatment versus 0 cases with fulvestrant monotherapy. In order to further characterise the risk of QT prolongation, relevant data from the CAPItello-290 study will be provided (Recommendation).

Thus, for patients with frequent and relevant concomitant diseases, e.g. diabetes or cardiac diseases or concomitant medication impacting QT-interval, there are very relevant safety concerns that need to be outweighed by substantial benefit. The exclusion of such patients from the CAPITello-291 study is reflected in sections 4.4 and 5.1 of the SmPC.

3.7.2. Balance of benefits and risks

The benefit in the PIK3CA/AKT1/PTEN altered population has been established in the pivotal study with more than doubling the median PFS time. This benefit is robust and supported by the mature data from the supportive FAKTION study. The benefits of capivasertib outweigh the risks from the combination treatment with fulvestrant.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of Truqap is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Truqap is favourable in the following indication:

TRUQAP is indicated in combination with fulvestrant for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine-based regimen (see section 5.1).

In pre- or perimenopausal women, TRUQAP plus fulvestrant should be combined with a luteinising hormone releasing hormone (LHRH) agonist.

For men, administration of LHRH agonist according to current clinical practice standards should be considered.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that capivasertib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.