2. SYNOPSIS

Study Centres

The study was conducted at 5 sites in the United States.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effect of capivasertib on the PK of midazolam	• AUCinf and Cmax of midazolam in the absence of capivasertib (C1D1) and during intermittent capivasertib treatment (4 days on/3 days off) including a 3rd day off-capivasertib and 4th day on-capivasertib
Secondary	
• To further describe the PK of midazolam alone and in combination with capivasertib	• AUClast, t½λz, tmax of midazolam in the absence of capivasertib (C1D1) and during intermittent capivasertib treatment (4 days on/3 days off) including a 3rd day off-capivasertib and 4th day on-capivasertib
• To describe the PK of capivasertib following repeated doses	• Ctrough of capivasertib and its glucuronide metabolite at C1D9, and C1D13 • Cmax, AUCτ, t½λz, and tmax of capivasertib and its glucuronide metabolite; and CL/F of capivasertib

Objectives	Endpoints
• To examine the safety and tolerability of capivasertib (with or without the use of standard of care) and in combination with midazolam	• Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory, and ECG. Assessments related to AEs cover: - Occurrence/frequency - Relationship to capivasertib and midazolam, as assessed by Investigator - CTCAE grade - Seriousness - Death - AEs leading to discontinuation of capivasertib - AEs leading to dose interruption of capivasertib - AEs leading to dose reduction of capivasertib - AESIs - Other significant AEs Vital signs parameters include systolic and diastolic blood pressure, pulse, and body temperature. Laboratory parameters include clinical chemistry and haematology parameters, as well as urinalysis, glucose, HbA1c, and lipid profile. ECG parameters include PR, RR, QRS, QT, and QTcF intervals and an overall evaluation.

Objectives and endpoints are presented as defined in CSP v 2.0 (Appendix 16.1.9).
AE = Adverse event; AESI = Adverse event of special interest; AUCinf = Area under the plasma concentration-time curve from zero to infinity; AUClast = Area under the plasma concentration-time curve from zero to last observed timepoint; AUCτ = Area under plasma concentration-time curve in the dose interval; C = Cycle; CL/F = Apparent total body clearance of drug from plasma after extravascular administration; Cmax = Maximum observed plasma (peak) drug concentration; CTCAE = Common Terminology Criteria for Adverse Events; Ctrough = observed trough plasma drug concentration; D = Day; ECG: = Electrocardiogram; HbA1c = Glycosylated haemoglobin; PK = Pharmacokinetic(s); QTcF = Corrected QT interval using Fridericia's formula; t½λz = Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve; tmax = Time to reach maximum observed (peak) plasma concentration.

Study Design

This was a 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.

Part A of the study consisted of a Screening period and 3 treatment periods (midazolam alone, capivasertib alone, and midazolam + capivasertib). For each patient, the total duration of participation in Part A was up to 43 days (or extended), including a Screening period of up to 28 days, a treatment period of 15 days and potential extension (in case of Part A extension to manage any tolerability or in case of protocol deviations [PD]).

During Part A, the PK profile of midazolam were determined in the absence of capivasertib and during intermittent capivasertib treatment (4 days on/3 days off) including on a 3rd day off-capivasertib and a 4th day on-capivasertib. The PK of capivasertib were also assessed to confirm steady state and determine the PK profile of capivasertib at steady state. Safety and tolerability were assessed, and safety assessments related to midazolam dosing were performed in the Part A extension, as applicable.

During Part A, all patients received capivasertib treatment (4 days on/3 days off); however, at the Investigator's discretion, oestrogen receptor positive breast cancer patients also received fulvestrant in addition to capivasertib and midazolam.

During Screening, local testing of phosphoinositide 3 kinase/serine/threonine specific protein kinase/phosphatase and tensin homolog (PIK3/AKT/PTEN) biomarker status was collected for patients where a test result was available. During Part A, an optional tumour sample was collected for exploratory analyses.

Patients who completed Part A without disease progression or unacceptable toxicity, and who were considered likely to continue to benefit from further capivasertib treatment (with or without certain standard of care treatment) in the opinion of the Investigator entered Part B of the study.

Part B of the study consisted of an extended treatment period with capivasertib with or without certain standard of care treatment followed by a 30-day safety follow-up. Each patient continued to receive capivasertib until disease progression or until any other discontinuation criteria were met.

During Part B, patients with no alterations in the PI3K/AKT/PTEN pathway (or unknown mutational status) were recommended to receive capivasertib in combination with standard of care (fulvestrant, paclitaxel, docetaxel, abiraterone, or olaparib), at the Investigator's discretion. Patients who harboured alterations in the PI3K/AKT/PTEN pathway, were eligible to receive capivasertib monotherapy or capivasertib in combination with standard of care treatment, at the Investigator's discretion.

During Part B, the efficacy of capivasertib was evaluated based on the assessment of tumour response according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, exploratory biomarker samples were collected, NGS could be performed, and safety and tolerability of capivasertib (with or without certain standard of care treatment) were assessed.

Target Population and Sample Size

Approximately 33 to 40 patients were to be screened, such that approximately 23 to 29 patients were planned to be assigned to study intervention and 14 evaluable patients completed Part A of the study.

Patients included in this study were at least 18 years of age at the time of signing the informed consent. Eligible patients had documented evidence of locally advanced inoperable or metastatic solid tumours, who were suitable for capivasertib treatment and had an Eastern Cooperative Oncology Group/World Health Organization (ECOG/WHO) performance status 0 to 1 with no deterioration over the previous 2 weeks and minimum life expectancy of 12 weeks, as assessed at Day -1. Patients had at least one lesion (measurable and/or non-measurable) that was accurately assessed at baseline by computed tomography (CT)/magnetic resonance imaging (MRI) or plain X-ray and was suitable for repeated assessment.

Patients were not eligible to participate if they received radiotherapy within 4 weeks of the first dose of capivasertib and/or radiotherapy with a limited field of radiation for palliation within 2 weeks prior to study intervention initiation, had major surgery (excluding placement of vascular access) within 4 weeks of the first dose of capivasertib. Patients were excluded from the study if they had any unresolved toxicity from prior therapies higher than common terminology criteria for adverse events (CTCAE) Grade 2 or any unresolved toxicity that may have interfered with PK assessment at the time of study intervention initiation, had any cardiac related exclusion criteria at Screening, or had any clinically significant abnormalities of glucose metabolism at Screening.

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

Intervention name	Capivasertib			Midazolam
Type	Drug			Drug
Dose formulation	Tablet			Syrup
Unit dose strength(s)	200 mg	160 mg	200 mg	[redacted] mg/mL
Dosage level(s)	Starting dose: 400 mg (2 tablets) bid	Reduced dose 1: 320 mg (2 tablets) bid	Reduced dose 2: 200 mg (1 tablet) bid	1 mg
	Given as an intermittent schedule (4 days on/3 days off) from C1D2 until discontinuation.			Single doses at C1D1, C1D8, and C1D12 [a]
Route of administration	Oral			Oral
Use	Experimental			Challenge agent
IMP and NIMP	IMP			NIMP

Sourcing	Supplied by AstraZeneca	Not supplied by AstraZeneca. Obtained locally.
Packaging and labelling	Drug was provided in high density polyethylene bottles. Each bottle was labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement.	Drug was obtained by sites in commercially available packaging
Batch/Lot numbers	CCI [redacted]	NA

[a] Part A of the study could have been extended to allow the administration of midazolam on a rescheduled C1D8 and C1D12 visit; thus, rescheduling of visits, midazolam dosing, and associated full PK profile collection could have been adapted in agreement with the Investigator and Sponsor.

bid = Twice daily; C = Cycle; D = Day; IMP = Investigational medicinal product; NIMP = Non-investigational medicinal product; NA = Not applicable; PK = Pharmacokinetic(s).

Duration of Treatment

For each patient, the total duration of participation in Part A of the study was expected to be up to 43 days (but could have been extended in case of Part A extension), including a Screening period of up to 28 days, a treatment period of 15 days, and a potential Part A extension. For Part B, each patient continued to receive capivasertib (with or without certain standard of care treatment) until disease progression or any other discontinuation criteria were met.

Statistical Methods

The primary PK endpoints, the area under the plasma concentration-time curve from zero to infinity (AUCinf) and the maximum observed plasma (peak) drug concentration (Cmax) of midazolam in the absence of capivasertib at Cycle 1 Day 1 (C1D1) and during intermittent capivasertib treatment (4 days on/3 days off) including a 3rd day off-capivasertib and a 4th day on-capivasertib, were analysed using a mixed effects model following a natural logarithmic transformation of the PK parameters with fixed effect for day and random effect for patient.

The least square geometric means (LSGmeans) for the treatment effects and the corresponding 2-sided 95% confidence intervals (CIs), as well as the ratios of LSGmeans of test treatment (3rd day off-capivasertib) and reference treatment (C1D1) and test treatment (4th day on-capivasertib) and reference treatment (C1D1) with 2-sided 90% CI were estimated.

The number of patients was selected to gain sufficient precision for the 90% CI of the LSGmeans ratio of AUCinf and Cmax, while exposing as few patients as possible to study drugs and procedures.

All listings, summary tables, and figures of PK concentrations and parameters, as well as all statistical analyses were presented for the pharmacokinetic analysis set, unless otherwise indicated.

All analyses of safety and tolerability outcomes were performed on the full analysis set (which is the same as the safety analysis set). The results of the assessments were listed and the observed values and changes from baseline were summarised by means of descriptive statistics per visit and/or relevant treatment periods.

Study Population

A total of 28 patients were enrolled in the study and of these 21 started the study intervention(s) and were included in the PKS and full analysis set (FAS). Seven patients were not dosed because of screen failure.

A total of 10 (47.6%) patients completed the study and 11 (52.4%) patients discontinued the study, mostly due to death and progressive disease (4 patients each). Two patients had confirmed COVID-19 infection after dosing and no patient died due to COVID-19 infection.

A total of 15 (71.4%) patients had at least one important PD during the study. None of the identified important PDs were considered to have a major impact on the study results and conclusions. No patients had COVID-19 related important PDs.

Most patients were females (14 [66.7%] patients) and the age ranged from 38 to 77 years for all patients. Most patients (13 [61.9%] patients) had ECOG performance status score 0, and the most common patients' primary tumour locations were colon and uterus.

The reported medical history and medications taken prior and during the study were generally typical of the co-morbidities seen in a population of patients with advanced solid tumours and all but one patient (20 [95.2%]) received previous anticancer regimens.

This patient population was considered to be adequately representative of the target population for the study treatment.

Summary of Pharmacokinetic Results

- On the 4th on day of intermittent capivasertib treatment (C1D12), statistical analysis showed an increase in midazolam exposure in the presence of capivasertib. Co-administration of capivasertib increased midazolam exposure based on AUCinf, with a geometric mean ratio (90% CI) of 175.4% (150.0%, 205.2%), which exceeds the threshold of 1.25-fold for the definition of a mild CYP3A inhibitor. Peak exposure also increased with a geometric mean ratio (90% CI) for Cmax of 125.3% (107.8%, 145.6%).
- On the 3rd off day of intermittent capivasertib treatment (C1D8), there was a trend to increased exposure based on AUCinf and Cmax, with geometric mean ratios (90% CI) of 113.0% (97.01%, 131.7%) and 114.7% (99.04%, 132.8%).

Summary of Efficacy Results

- The median progression-free survival (PFS) was CCI in the overall population and the PI3K altered sub-population CCI CCI The proportion of patients who were alive and progression-free (PFS rates) at 3, 6, and 9 months CCI in the overall population and was CCI in the PI3K altered sub-population.
- CCI of the patients had disease progression or died without progression CCI Of these, CCI patients were on treatment at the time of progression while CCI patients discontinued treatment prior to progression.
- A CCI of patients CCI had a confirmed objective response, with an ORR of CCI patients were in the PI3K altered sub-population.
- The median time from the date of first documented response until date of documented progression or death in the absence of disease progression (DoR), was CCI CCI
- At 24 weeks, [redacted] patients had a confirmed CR or PR or had a stable disease without subsequent cancer therapy after date of first dose, showing a CBR of CCI CCI).

Summary of Safety Results

- Overall, AEs related to study intervention(s) were manageable and capivasertib treatment was tolerated in this heavily pre-treated population of patients with advanced solid tumours. The safety data were consistent with the known safety profile of capivasertib when administered with or without the use of standard of care, and in combination with midazolam.
- The most frequently reported (> 10% of patients) were Diarrhoea (16 [76.2%] patients), Nausea, Fatigue (7 [33.3%] patients each), Anaemia, Hyperglycaemia (6 [28.6%] patients each), Decreased appetite, Hypokalaemia (5 [23.8%] patients each), Hyponatraemia, Dyspnoea, Rash, Hypotension (4 [19.0%] patients each), and Constipation, Blood creatinine increased, Lymphocyte count decreased, Weight decreased, Dehydration, Arthralgia and Asthenia (3 [14.3%] patients each).
- There were 12 (57.1%) patients who experienced CTCAE Grade 3 AEs. One patient reported CTCAE Grade 4 Thrombocytopenia and one patient experienced Sepsis leading to death CTCAE Grade 5.
- Seventeen (81.0%) patients experienced AEs that were assessed by the Investigator as related to capivasertib alone; for 11 (52.4%) patients the reported AE was Diarrhoea. For 6 (28.6%) patients, AEs were considered as related to both capivasertib and midazolam, with most PTs reported in single patients. One event (PT Nausea) was assessed as related to midazolam.
- Four (19.0%) patients died during the study. One patient experienced an AE with outcome of death (PT Sepsis, assessed as not related to any of the study interventions),

2 patients had deaths that were assessed by the Investigator to be related to the disease under investigation only, and one death was categorised as 'other deaths'.

- Five (23.8%) patients experienced on-treatment SAEs during the study (PTs of Thrombocytopenia, Large intestinal obstruction, Asthenia, Sepsis, Blood bilirubin increased, and Rash).
- Three patients experienced AEs leading to permanent discontinuation of capivasertib only. No permanent discontinuation was related to midazolam, or both capivasertib and midazolam.
- AESIs pertaining to 'Hyperglycaemia' and 'Rash' were reported in a total of 13 (61.9%) patients (8 and 6 patients, respectively). No AESIs pertaining to 'Torsade de pointes/QT Prolongation' were reported.
- There were transient fluctuations observed over time for clinical chemistry values, vital signs, and ECG parameters during the study. Overall, no clinically meaningful trends were observed for clinical laboratory values, vital signs, ECGs, physical findings, and other observations related to safety.

Conclusions

- Using midazolam as a probe substrate, capivasertib was demonstrated to be a mild inhibitor of CYP3A, when capivasertib was administered on an intermittent schedule 400 mg twice daily, 4 days on, 3 days off. The midazolam geometric mean ratio (GMR) of AUC were 1.13 (90% CI: 0.97, 1.32) and 1.75 (90% CI: 1.50, 2.05) on the 3rd off-dosing day (C1D8) and the 4th on-dosing day (C1D12) of capivasertib, respectively, compared to when midazolam was given alone prior to capivasertib (C1D1).
- Overall, the safety and tolerability profile following treatment with capivasertib or capivasertib in combination with midazolam was consistent with the known safety profiles of capivasertib and midazolam in a population of patients with advanced solid tumours. No new clinically significant findings that may alter the current understanding of the capivasertib safety profile as monotherapy or in combination with midazolam were identified.
- Results for the exploratory efficacy objectives (PFS, ORR, DoR, and CBR) were CCI Due to the CCI , and the CCI . The CCI .