# Clinical Study Report

## 1 TITLE PAGE

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

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| **Investigational Medicinal Products:** | Capivasertib (AZD5363) tablet<br>Rabeprazole<br>Famotidine (if required) |
| **Indication Studied:** | Solid and hematological malignancies |
| **Parexel Study Number:** | CCI [redacted] |
| **Sponsor Study Number:** | D3614C00005 |
| **EudraCT Number:** | 2021-000836-74 |
| **Development Phase:** | Phase I |
| **Sponsor:** | AstraZeneca AB<br>151 85 Södertälje<br>Sweden |
| **Investigator Name and Address:** | PPD<br>Parexel Early Phase Clinical Unit Berlin<br>CCI [redacted]<br>[redacted]<br>14050 Berlin Germany |
| **Study Duration:** | 26 July 2021 (first subject first visit) to 04 May 2022 (last subject last visit) |
| **Version and Date of Report:** | Final 1.0, dated 09 September 2022 |

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines. The essential documentation related to this study has been retained by relevant parties.

# 2 SYNOPSIS

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| **Title of Study:** | 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 | |
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| **Sponsor:** | AstraZeneca AB<br>151 85 Södertälje<br>Sweden | |
| **Principal Investigator:** | PPD | |
| **Study Center:** | Parexel Early Phase Clinical - Berlin | |
| **Publication:** | None | |
| **Study Duration:** | First subject first visit:<br>26 July 2021 | Last subject last visit:<br>04 May 2022 |

**Study Objectives:**

**Primary objectives:**

- To assess the effect of food on the pharmacokinetics (PK) of capivasertib.
- To assess the effect of the acid reducing agent(s) rabeprazole and famotidine (if required), on the PK of capivasertib.

**Secondary objectives:**

- To assess the safety and tolerability of capivasertib when administered alone under fed and fasted conditions, and in combination with acid reducing agent(s) rabeprazole and famotidine (if required).

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**Study Design:**

This study was a two-part, open-label, randomized, crossover study in healthy subjects, performed at 1 study center. The study was divided into 2 parts: Part 1 (included 3 treatment periods) and Part 2 (included 3 treatment periods in a new group of healthy subjects).

**Part 1**

Part 1 of the study comprised:

- A screening period of maximum 28 days.
- Three treatment periods during which subjects were resident from the morning of Day -1 (Day -4 for subjects receiving rabeprazole [Treatment C]) and discharged after the last PK sample collection, 48 hours after dosing of capivasertib of each treatment period.
- There was a minimum washout period of 14 days between each capivasertib dose administration.
- A final visit 7 to 14 days after the last capivasertib PK sample in Treatment Period 3.

On Day -4 of Treatment Period 1, 24 subjects were randomized to one of 6 treatment sequences: ABC, ACB, BAC, BCA, CAB or CBA. Each cohort (treatment sequence) had at least 3 subjects. All subjects received 3 single doses of CCI capivasertib as described below:

- Treatment A: Single oral dose of CCI capivasertib, overnight fasted state (reference treatment).
- Treatment B: Single oral dose of CCI capivasertib, fed state (after a high-fat, high-calorie meal).
- Treatment C: Twice daily oral doses of CCI rabeprazole for 3 days (Days -3 to -1) and a single dose on the morning of Day 1 + a single oral dose of CCI capivasertib under fasted conditions on Day 1.

**Part 2**

Part 2 of the study followed a similar design to Part 1 and was initiated based on the findings from Part 1.

Part 2 of the study comprised:

- A screening period of at least 28 days.
- Three treatment periods during which subjects were resident from the morning of Day -1 and were discharged after the last PK sample collection 48 hours after dosing of capivasertib of each treatment period consistent with Part 1.
- There was a minimum washout period of 14 days between each capivasertib dose administration.
- A final visit 7 to 14 days after the last capivasertib PK sample in Treatment Period 3.

The interim results from Part 1 indicated a potentially clinically relevant food interaction only and therefore Treatments D, E, and F were studied in Part 2. On Day -1 of Treatment Period 1, 24 subjects were randomized to one of 6 treatment sequences: DEF, DFE, EDF, EFD, FDE, FED. Each cohort (treatment sequence) had at least 3 subjects. All subjects received 3 single doses of CCI capivasertib as described below:

- Treatment D: Single oral dose of CCI capivasertib, overnight fasted state (reference treatment).
- Treatment E: Single oral dose of CCI capivasertib under fed conditions (after a low-fat, low-calorie meal).
- Treatment F: Single oral dose of CCI capivasertib under partially fasted conditions (food restricted from 2 hours prior to dosing until 1 hour after dosing).

**Study Subjects:**

| **Planned for Inclusion:** | **Randomized:** | **Completed Study:** | **Evaluable subjects:** |
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| Total consented: 75 subjects | Part 1: 24 subjects<br>Part 2: 24 subjects | Part 1: 23 subjects<br>Part 2: 24 subjects | Part 1: 22 subjects<br>Part 2: 24 subjects |

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| **Main Inclusion Criteria:**<br>For both Parts 1 and 2, the study included healthy, non-smoking male and female subjects (females were of non-childbearing potential) aged 18 to 58 (inclusive) years who had a body mass index between 18.0 to 29.9 kg/m$^2$ (inclusive) for males, and 18 to 32 kg/m$^2$ (inclusive) for females, and weighed at least 50 kg and no more than 100 kg (inclusive). | | |
| **Investigational Medicinal Products (IMP):** Capivasertib tablet and rabeprazole tablet | | |
| **Properties** | **Capivasertib** | **Rabeprazole** |
| Supplier: | AstraZeneca | Hubertus Pharmacy |
| Formulation: | Film-coated tablet | Gastro-resistant tablet |
| Strength/concentration: | CCI | CCI |
| Dose: | CCI | CCI |
| Route of administration: | Oral | Oral |
| Specific device for drug administration, if applicable: | Not applicable | Not applicable |
| Regimen: | Single dose on Day 1 | Twice daily, approximately 12 hours apart for 3 days (Days -3 to -1) and a single dose on the morning of Day 1 |
| Special handling requirements: | NA | NA |
| Availability of the IMP: | Was shipped to Hubertus Pharmacy when Regulatory Authority (Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM]) approval was in place and shipped to site by Hubertus Pharmacy when Regulatory Authority (BfArM) and Ethics Committee (EC) approvals were in place | Was shipped to site when Regulatory Authority (BfArM) and EC approvals were in place |
| Batch/Manufacturing Lot Number (expiry date): | CCI | CCI |
| **Treatments:** | | |
| **Part 1** | | |
| Treatment A | Single oral dose of CCI capivasertib, overnight fasted state (reference treatment) | |
| Treatment B | Single oral dose of CCI capivasertib, fed state (after a high-fat, high-calorie meal) | |
| Treatment C | Twice daily oral doses of CCI rabeprazole for 3 days (Days -3 to -1) and a single dose on the morning of Day 1 + a single oral dose of CCI capivasertib under fasted conditions on Day 1. | |

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| **Part 2** | |
| Treatment D | Single oral dose of CCI capivasertib, overnight fasted state (reference treatment) |
| Treatment E | Single oral dose of CCI capivasertib under fed conditions (after a low-fat, low-calorie meal). |
| Treatment F | Single oral dose of CCI capivasertib under partially fasted conditions (food restricted from 2 hours prior to dosing until 1 hour after dosing). |

**Duration of Treatment:**

In both Part 1 and Part 2, each subject was expected to be involved in the study for approximately 9 to 10 weeks.

**Treatment Compliance:**

Dosing took place at the study center (Parexel Early Phase Clinical Berlin, Germany). The administration of all IMPs was recorded in ClinBase™. Compliance was assured by direct supervision and witnessing of IMP administration. After IMP administration, a check of the subject's mouth and hands was performed.

**Criteria for Evaluation:**

**Pharmacokinetic Parameters:**

- PK parameters of capivasertib including, but not limited to Cmax, AUCinf and AUClast in the fed and fasted state
- PK parameters of capivasertib including, but not limited to Cmax, AUCinf and AUClast alone and in combination with acid reducing agent(s)

**Safety Variables:**

Assessment of AEs, laboratory variables (haematology, clinical chemistry, and urinalysis), vital signs (systolic and diastolic blood pressure, pulse, respiratory rate), 12-lead ECGs, physical examination, and body temperature

**Statistical Methods:**

**Determination of Sample Size:**

Based on the estimated true intra-subject CV for Cmax, AUClast and AUCinf of capivasertib of 22%, 18 subjects are needed to achieve a relative precision of 1.4 (ratio between the upper and lower limits of the 90% confidence interval [CI]), with a power of 80%. This corresponds to a 90% CI of 0.85 to 1.18 if the observed ratio is 1.00, or a 90% CI of 0.63 to 0.89 if the observed ratio is 0.75. To account for potential discontinuations, 24 subjects were to be included in each part of the study. In Part 1, 24 subjects were to be randomized to 6 sequences of Williams design for 3 periods and 3 treatments: ABC, BCA, CAB, ACB, BAC, and CBA, in order to ensure at least 18 subjects with PK data from both test and reference treatments. In Part 2, 24 subjects were randomized to 6 sequences of 3 treatments: DEF, DFE, EDF, EFD, FDE, FED, in order to ensure at least 18 subjects with PK data from both test and reference treatments.

**Presentation and Analysis of Pharmacokinetic Data:**

A listing of PK blood sample collection times, including derived sampling time deviations and all reportable concentrations, were presented for capivasertib for all dosed subjects. An additional listing of PK concentrations versus time was presented in table format based on the PK analysis set.

Plasma capivasertib concentrations were summarized for the PK analysis set for each time point by study part and treatment using CSP scheduled times and appropriate descriptive statistics.

All reportable PK parameters from the noncompartmental PK analysis were listed for all subjects dosed.

Plasma PK parameters were summarized for the PK analysis set by study part and treatment.

The PK concentration and parameter data were presented according to the most recent version of the AstraZeneca Corporate CSRHLD reporting standards version 3.4, that includes applicable descriptive statistics, handling of individual concentrations below the lower limit of quantification (LLOQ) for listings, descriptive statistics and figures, and precision and rounding rules for concentrations and PK parameter data.

Individual plasma concentrations versus actual elapsed time after dose were plotted on both the linear and semi-logarithmic scale with all dosed treatments overlaid on the same plot and separate plots for each subject. Plots were based on all dosed subjects.

Combined individual plasma concentration versus actual times were plotted based on the PK analysis set on both the linear and semi-logarithmic scale, with all subjects for the same study part and treatment overlaid on the same plot. Plots were based on the PK Analysis Set.

Geometric mean plasma concentration (-/+gSD) versus nominal sampling time were plotted on both the linear scale and semi-logarithmic (no gSD presented) with all treatments overlaid on the same plot. Plots were based on the PK analysis set. Focus plots were provided if there were no clear distinction among profiles.

The PK analysis set consisted of all subjects in the safety analysis set who received at least 1 dose of capivasertib and who have at least 1 quantifiable post-dose plasma concentration.

Pharmacokinetic concentrations and parameters were summarized for each study part and treatment using descriptive statistics. The descriptive statistics included: n, geometric mean, geometric coefficient of variation, arithmetic mean, arithmetic SD, median, minimum and maximum. For tmax and tlag, only n, median, minimum and maximum were presented. The geometric mean ratios of Cmax, AUCinf and AUClast were calculated for each treatment comparison (Test treatment versus Reference treatment):

- Treatment B versus Treatment A (Part 1).
- Treatment C vs Treatment A (Part 1).
- Treatment E vs Treatment D (Part 2).
- Treatment F vs Treatment D (Part 2).
- Treatment E vs Treatment F (Part 2).
- Treatment B (Part 1) vs Treatment F (Part 2).

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Analyses of the PK parameters Cmax, AUCinf and AUClast were performed within each part using a mixed effects model following a natural logarithm transformation of the PK parameters, with fixed effects for treatment, treatment period and sequence and subject nested within sequence as a random effect. For the between part comparison (Treatment B vs Treatment F), sequence is not relevant and was thus dropped from the model.

For the effect of the acid reducing agent, the least-squares (LS) geometric means and the corresponding 2-sided 95% CIs, as well as ratios of LS geometric means together with 2-sided 90% CIs of test treatment (capivasertib + acid reducing agent) and reference treatment (capivasertib alone) were estimated and presented.

For the effect of food, the LS geometric means and the corresponding 2-sided 95% CIs as well as ratios of LS geometric means together with 2-sided 90% CIs of test treatment (capivasertib under fed conditions) and reference treatment (capivasertib under fasted conditions) were estimated and presented.

**Presentation and Analysis of Safety Data:**

All subjects who received at least 1 dose of capivasertib and for whom any safety post-dose data are available were included in the safety analysis for the study.

All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarized using descriptive statistics (n, mean, SD, min, median, max) by treatment. Categorical variables were summarized in frequency tables (frequency and proportion) by treatment/dose group. The analysis of the safety variables was based on the safety analysis set.

Adverse events were summarized by Preferred Term (PT) and System Organ Class (SOC) using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary. Furthermore, listings of serious adverse events (SAEs) and AEs that led to the discontinuation of IMP were made and the number of subjects who had any AE, SAEs, AEs that led to the discontinuation of IMP, and AEs with severe intensity were summarized. Adverse events that occurred from time of informed consent before dosing were reported separately.

Tabulations and listings of data for vital signs, clinical laboratory tests and ECGs (listings only) were presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared with the baseline assessment was reported as an AE. Data was summarized for the observed values at each scheduled assessment, together with the corresponding changes from the baseline when baseline was defined. Clinical laboratory data was reported in Système International units in the CSR.

Out-of-range values for safety laboratory and ECGs were flagged in individual listings as well as summarized descriptively using agreed standard reference ranges and/or extended reference ranges (e.g., AZ, program, or laboratory ranges).

**Protocol Deviations:**

**Part 1**

Due to delayed implementation of informed consent document (ICD) version 3.0, 22 (91.7%) subjects did not provide appropriate Informed Consent for Part 1. These subjects were consented on ICD version 2.0 and were not re-consented on ICD version 3.0 on enrolment. All of these subjects who were randomized and received at least one dose of capivarsetib were re-consented on ICD version 3.0 at a later date and the Ethics Committee was informed. A File Note was put in place to document the deviation and re-consenting.

**Part 2**

There were no important protocol deviations in this study during Part 2.

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**Pharmacokinetic Results:**

**Effect of food**

- Systemic exposure to capivasertib was increased when dosed with a high-fat, high-calorie meal compared to when dosed after an overnight fast, with GMRs and 90% CIs of 1.233 (1.078, 1.410), 1.323 (1.223, 1.431) and 1.327 (1.226, 1.436) for Cmax, AUCinf and AUClast, respectively.
- Systemic exposure to capivasertib was similar for Cmax and equivalent for AUC when dosed with a low-fat, low-calorie meal compared to when dosed after an overnight fast, with GMRs and 90% CIs of 1.208 (0.9864, 1.479), 1.144 (1.048, 1.249) and 1.150 (1.050, 1.260) for Cmax, AUCinf and AUClast, respectively.
- Systemic exposure to capivasertib increased when dosed under partially fasted conditions compared to when dosed after an overnight fast, with GMRs and 90% CIs of 1.397 (1.131, 1.724), 1.193 (1.088, 1.307) and 1.201 (1.091, 1.321) for Cmax, AUCinf and AUClast, respectively.
- Systemic exposure to capivasertib was similar in Part 1 subjects dosed with a high-fat, high-calorie meal compared to that in Part 2 subjects dosed under partially fasted conditions, with GMRs and 90% CIs of 0.8536 (0.6977, 1.044), 1.132 (0.9917, 1.293) and 1.134 (0.9919, 1.297) for Cmax, AUCinf and AUClast, respectively.
- Systemic exposure to capivasertib was similar for Cmax and equivalent for AUCinf and AUClast when dosed with a low-fat, low-calorie meal compared to when dosed under partially fasted conditions, with GMRs and 90% CIs of 0.8647 (0.7024, 1.064), 0.9590 (0.8760, 1.050) and 0.9578 (0.8719, 1.052) for Cmax, AUCinf and AUClast, respectively.

**Effect of acid reducing agent**

- Systemic exposure to capivasertib was decreased for Cmax and equivalent for AUCinf and AUClast when dosed fasted in the presence of the acid reducing agent rabeprazole compared to when dosed after an overnight fast in the absence of an acid reducing agent, with GMRs and 90% CIs of 0.7323 (0.6393, 0.8389), 0.9378 (0.8658, 1.016) and 0.9316 (0.8597, 1.010) for Cmax, AUCinf and AUClast, respectively.

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**Safety Results:**

**Part 1**

Single oral doses of CCI capivasertib administered in an overnight fasted state (Treatment A), fed state (Treatment B – high-fat, high-calorie meal), and co administered with CCI rabeprazole in an overnight fasted state (Treatment C) were safe and well tolerated in this study.

These conclusions are based on the following results:

- Overall, 14 (60.9%) subjects had at least 1 AE.
- Diarrhoea was the most commonly reported AE in any treatment group (8 [34.8%] subjects), followed by nausea (5 [21.7%] subjects).
- Overall, 11 (47.8%) subjects had at least 1 AE considered possibly related to IMP according to Investigator's causality assessment.
- The majority of AEs were grade 1 (mild) in severity (12 subjects [52.2%]) and there were no grade 3 (severe) AEs.
- There were no fatal events or other SAEs.
- One subject reported the AE of liver function test increased that was mild in severity and not possibly related to IMP as per Investigator's assessment. The IMP was discontinued due to this AE.
- No clinically relevant findings were observed for laboratory results (other than relating to the AE of liver function test increased), vital signs, physical examinations, and ECGs and no safety concerns were raised.
- There was no impact on study conduct or safety of subjects due to COVID-19.

**Part 2**

Single oral doses of CCI capivasertib administered in an overnight fasted state (Treatment D), fed state (Treatment E – low-fat, low-calorie meal), and in a partially fasted state (Treatment C – food restricted from 2 hours prior to dosing until 1 hour after dosing) were safe and well tolerated in this study.

These conclusions are based on the following results:

- Overall, 18 (75.0%) subjects had at least 1 AE.
- Diarrhoea was the most commonly reported AE in any treatment group (13 [54.2%] subjects), followed by COVID-19 (3 [12.5%] subjects).
- Overall, 14 (58.3%) subjects had at least 1 AE considered possibly related to IMP according to Investigator's causality assessment.
- The majority of AEs were grade 1 (mild) in severity (17 subjects [70.8%]) and there were no grade 3 (severe) AEs.
- There were no fatal events or other SAEs.
- No clinically relevant findings were observed for laboratory results, vital signs, physical examinations, and ECGs and no safety concerns were raised.
- Two subjects discontinued IMP due to mild AEs of COVID-19.

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**Conclusions:**

**Pharmacokinetics**

- Dosing of capivasertib tablets after a high-fat, high-calorie meal resulted in higher AUC and higher Cmax, compared to when dosed after an overnight fast, but similar AUC and Cmax compared to when given partially fasted (no food from 2 hours prior to dosing until 1 hour after dosing).
- Dosing of capivasertib tablets after a low-fat, low-calorie meal resulted in equivalent AUC and similar Cmax, both when compared to dosing after an overnight fast and when compared to dosing partially fasted.
- Dosing of capivasertib tablets in the presence of rabeprazole resulted in equivalent AUC but lower Cmax, compared to when capivasertib was given alone.

**Safety**

- Overall, single oral doses of capivasertib administered in an overnight fasted state, high-fat, high-calorie fed state, low-fat, low-calorie fed state, and in a partially fasted state, were safe and well tolerated in this study.
- Co-administration of rabeprazole with capivasertib was safe and well tolerated in this study.
- No new safety concerns were found for the capivasertib treatments in this study.

**COVID-19 Pandemic**

The COVID-19 pandemic was not judged to meaningfully impact the overall quality of the study, including the conduct, data, and interpretation of results.

Version and Date of Report: Final 1.0, dated 09 September 2022

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