2 SYNOPSIS

Title of Study:	An Open-label, Fixed Sequence Study in Healthy Subjects to Assess the Pharmacokinetics of Capivasertib When Administered Alone and In Combination with Itraconazole	
Study Numbers:	Parexel Study No.: CCI Sponsor Study No.: D3614C00004	
Investigational Medicinal Products:	Capivasertib (AZD5363) tablet Itraconazole hard capsule	
Study Type:	Drug-drug interaction	
Development Phase:	Phase 1	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	PPD	
Study Centre:	Parexel Early Phase Clinical Unit - Berlin	
Publication:	None	
Study Duration:	First subject first visit: 04 February 2021	Last subject last visit: 25 March 2021

Study Objectives:

Primary objectives:

- To assess the effect of itraconazole on the pharmacokinetics (PK) of capivasertib

Secondary objectives:

- To further characterise the effect of itraconazole on the PK of capivasertib and its major metabolite (AZ14102143)
- To further assess/monitor the safety and tolerability of capivasertib alone and in combination with itraconazole

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Study Design:

This study was an open-label, fixed sequence study in healthy subjects (females of non-childbearing potential), performed at a single study centre. The study comprised:

- A screening period of maximum 21 days.
- A fixed sequence of 3 treatment periods during which subjects were resident from the morning of the day before first dosing with capivasertib (Treatment Period 1, Day -1: admission) until at least 48 hours after last dosing with capivasertib (Treatment Period 3, Day 8: last capivasertib PK sample, followed by discharge).

  Treatment Period 1: Capivasertib only

  Eligible subjects were admitted to the study centre on Day -1. On Day 1, subjects received a single oral dose of capivasertib. Blood samples for capivasertib concentrations were collected at pre dose on Day 1 and post-dose up to 48 hours (Day 1 to Day 3).

  Treatment Period 2: Itraconazole pre-treatment (run-in) period

  On Day 3, subjects received itraconazole in the morning and in the evening. On Days 4 and 5, subjects received itraconazole in the mornings only.

  Treatment Period 3: Capivasertib and itraconazole in combination

  On Day 6, subjects received a single oral dose of capivasertib plus a dose of itraconazole concomitantly in the morning. On Day 7, subjects received itraconazole in the morning. Blood samples for capivasertib concentrations were collected at pre-dose on Day 6 and post-dose up to 48 hours (Day 6 to Day 8). After all procedures were completed and there were no safety concerns, subjects were discharged from the study centre.
- A Follow-up Visit at 7 to 14 days after the last capivasertib PK sample in Treatment Period 3.

There was no washout between Treatment Period 2 and Treatment Period 3. Subjects were resident continuously for the full duration of the treatment periods.

Study Subjects:

Planned for Inclusion:	**Completed Study:**
11 subjects	11 subjects

Main Inclusion Criteria:

Healthy non-smoking male and female subjects of non-childbearing potential aged 18 to 58 years with suitable veins for cannulation or repeated venepuncture. Subjects with a body mass index between 18 and 28.0 kg/m^2, inclusive, who weighed at least 50 kg and no more than 100 kg, inclusive.

Investigational Medicinal Product (Capivasertib):

Formulation:	**Strength/Concentrations:**	**Batch/Manufacturing Lot Number(s):**	**Expiry Date:**
Film-coated tablet	Capivasertib [redacted]	[redacted]	[redacted]

Investigational Medicinal Product (Itraconazole):

Formulation:	**Strength/Concentrations:**	**Batch/Manufacturing Lot Number(s):**	**Expiry Dates:**
Hard capsule	Itraconazole [redacted]	[redacted]	[redacted]

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		CCI	CCI

Duration of Treatment:

- Treatment Period 1: On Day 1 subjects received a single oral dose of capivasertib (CCI tablet).
- Treatment Period 2: On Day 3 subjects received a first oral dose of CCI hard capsules) itraconazole. CCI after first dosing with itraconazole, on the same day, subjects received a second oral dose of CCI hard capsules) itraconazole. On the mornings of Days 4 and 5, subjects received an oral dose of CCI hard capsules) itraconazole.
- Treatment Period 3: On Day 6 subjects received a single oral dose of capivasertib (CCI tablet) plus an oral dose of CCI hard capsules) itraconazole. On Day 7 subjects received an oral dose of CCI hard capsules) itraconazole CCI

Treatment Compliance:

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

Criteria for Evaluation:

Pharmacokinetic Parameters:

Primary: AUCinf and Cmax of capivasertib

Secondary: AUClast, tlag, tmax, t½λz, λz, CL/F, and Vz/F of capivasertib and AUCinf, M:P (AUCinf), Cmax, AUClast, tmax, t½λz, and λz of its major metabolite (AZ14102143)

Safety Variables:

Adverse events, clinical laboratory assessments (haematology, clinical chemistry [including blood glucose], and urinalysis), vital signs (systolic and diastolic blood pressure, pulse, tympanic temperature, respiratory rate), standard 12-lead electrocardiogram and physical examination.

Statistical Methods:

CCI [redacted]

Presentation and Analysis of Pharmacokinetic Data:

The PK analysis set consisted of all subjects who received at least 1 dose of capivasertib with at least 1 quantifiable plasma concentration post-dose for capivasertib.

All PK concentration and parameter summaries, and statistical analyses were presented for the PK analysis set, unless otherwise specified. The available concentration data and PK parameter data for any subjects excluded from the PK and/or statistical analysis were listed and presented in the individual figures of concentration versus time plots.

A listing of PK blood sample collection times (including nominal and actual sample times), derived sampling times and deviations as well as concentrations at each nominal time point were provided.

Plasma concentrations and PK parameters were summarised by treatment using appropriate descriptive statistics. Tabulations were provided for capivasertib and its major metabolite (AZ14102143).

Diagnostic parameters were summarised for each analyte by treatment using appropriate descriptive statistics.

Nominal times were used to present the PK concentration summary tables and corresponding gmean concentration-time figures.

Data from subjects excluded from the PK analysis set were included in the data listings, but not in the descriptive statistics or in the inferential statistics.

Presentation and Analysis of Safety Data:

The safety analysis set consisted of all subjects who received at least 1 dose of capivasertib and for whom any safety post-dose data were 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 summarised using descriptive statistics (number of subjects, mean, standard deviation, minimum, median, maximum) by treatment and overall. Categorical variables were summarised in frequency tables (frequency and proportion) by treatment and overall. The analysis of the safety variables was based on the safety analysis set, unless indicated otherwise.

Adverse events with onset (start date/time) or worsening after dosing in Treatment Period 1 up to and including the Follow-up Visit were summarised by system organ class and preferred term using Medical Dictionary for Regulatory Activities version 23.1 vocabulary.

Furthermore, listings of serious AEs (SAEs) and adverse events (AEs) that led to withdrawal were made and the number of subjects who had any AE, SAEs, AEs that led to withdrawal, and AEs with severe intensity (AEs with Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) were summarised. Adverse events were also summarised by maximum CTCAE grade and causally related to IMPs as assessed by the Investigator. Adverse events that occur before dosing were reported separately.

Tabulations of data for clinical laboratory tests and listings of data for clinical laboratory tests and electrocardiograms (ECGs) were presented. Any new or aggravated clinically relevant abnormal medical finding at a physical examination compared to the baseline assessment were reported as an AE. Data were summarised for the observed values at each scheduled assessment, together with the corresponding changes (and/or percentage change) from the baseline when baseline was defined. Clinical laboratory data were reported in the International System of Units in the clinical study report.

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Out-of-range values for clinical laboratory tests were flagged in individual listings as well as summarised descriptively using agreed standard reference ranges and/or extended reference ranges as indicated in the data management plan.

Protocol Deviations:

No important protocol deviations, including coronavirus disease 2019-related important protocol deviations, were identified in this study.

Pharmacokinetic Results:

- Repeat administration of itraconazole increased capivasertib exposure by 1.70-fold for Cmax (90% CI: 1.56, 1.86) and 1.95-fold for AUCinf (90% CI: 1.82, 2.10). Although an increase has been observed, the increase is below 2-fold and therefore capivasertib is not considered to be a sensitive or a moderate sensitive substrate, as defined by the Food and Drug Administration (FDA) (2020) and European Medicines Agency (EMA) (2012) drug-drug interaction guidances.
- The exposure to the metabolite AZ14102143 was 8.75-fold higher than exposure to capivasertib when capivasertib was given alone, and 5.77-fold when given in combination with itraconazole.

Safety Results:

Overall, 3 subjects (27.3%) experienced at least 1 AE during the study. Two subjects (18.2%) after receiving capivasertib in Treatment Period 1 and 2 subjects (18.2%) after receiving itraconazole in Treatment Period 2. No AEs were reported for any of the subjects after receiving a combination of capivasertib and itraconazole in Treatment Period 3.

In total, 5 AEs were reported and included 2 events of cough and single events of dyssomnia, back pain and acne. All reported AEs were considered mild in severity, except for the AE of back pain that was considered moderate in severity. All AEs resolved before the end of the study.

As per Investigator assessment there was 1 subject (9.1%) with an AE related to the IMP. Acne was reported by subject PPD on Day 4 (Treatment Period 2) after receiving itraconazole. The AE resolved without intervention.

No SAEs or AEs of special interest were reported. No AEs that led to discontinuation of IMP or the study, or with an outcome of death were reported.

No clinically relevant trends were observed for laboratory results and vital signs. No clinically significant abnormal ECG findings were reported, and no physical examination findings were reported as AEs.

There were no new safety signals observed when capivasertib was administered alone or in combination with itraconazole.

No new safety concerns were identified and capivasertib was generally well tolerated alone and in combination with itraconazole in healthy female subjects in this study.

Discussion and Conclusion:

- Repeat administration of itraconazole increased capivasertib exposure by 1.70-fold for Cmax (90% CI: 1.56, 1.86) and 1.95-fold for AUCinf (90% CI: 1.82, 2.10). Although an increase has been observed, the increase is below 2-fold and therefore capivasertib is not considered to be a sensitive or a moderate sensitive substrate, as defined by the FDA (2020) and EMA (2012) drug-drug interaction guidances.
- No new safety concerns were identified and capivasertib was generally well tolerated when administered alone and in combination with itraconazole in healthy female subjects in this study.

Version and Date of Report: Final 1.0, dated 20 September 2021

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.