2 STUDY SYNOPSIS

Name of Sponsor/Company: AstraZeneca AB	Name of Study Treatment: Capivasertib and [^{14}C]AZD5363 (Capivasertib)	Name of Active Ingredient: Capivasertib (AZD5363)

Title of Study: A Phase I Study to Investigate the Absolute Bioavailability, Absorption, Metabolism, Distribution and Excretion of [^{14}C]AZD5363 (Capivasertib) in Healthy Male Subjects

Principal Investigator: PPD

Study Centre: Quotient Sciences, Mere Way, Ruddington, Nottingham, NG11 6JS, UK

Publication (Reference): None**Studied Period:** 12 Apr 2022 to 12 Jul 2022

Phase of Development: I

Objectives:

Part 1

The primary objectives of Part 1 of the study were:

- To determine the absolute oral bioavailability of capivasertib
- To determine the pharmacokinetics (PK) of capivasertib and carbon-14 [^{14}C]AZD5363 (Capivasertib) in plasma

The secondary objective of Part 1 of the study was:

- To provide additional safety and tolerability information for capivasertib

Part 2

The primary objectives of Part 2 of the study were:

- To determine the pharmacokinetics of capivasertib in plasma and urine; and total radioactivity (TR) in plasma and whole blood
- To determine the mass balance recovery after a single oral dose of [^{14}C]AZD5363 (Capivasertib)
- To determine the routes and rates of elimination of [^{14}C]AZD5363 (Capivasertib)
- To evaluate the extent of distribution of total radioactivity into blood cells

The secondary objectives of Part 2 of the study were:

- To identify the chemical structure of each metabolite accounting for more than 10% of circulating total radioactivity or accounting for 10% or more of the dose in excreta[a]
- To provide additional safety and tolerability information for capivasertib

The exploratory objective of Part 2 of the study was:

- To perform metabolite profiling and structural identification from plasma, urine and faecal samples[a]

Parts 1 and 2

The exploratory objective of Parts 1 and 2 was:

- To collect and store DNA for future exploratory research into genes/genetic variations that may influence the pharmacokinetics or metabolism of capivasertib[b]

[a] Metabolite profiling and identification are reported separately from the clinical study report (CSR) as a standalone document.

[b] The exploratory pharmacogenetic analyses, if conducted, will be reported separately from the CSR.

Methodology:

This was a single centre, non-randomised, two-part, sequential dose, open-label study in healthy male subjects. It was planned that subjects would take part in both parts of the study. It was planned to enrol 8 subjects in a single group to ensure data in a minimum of 6 subjects in each study part.

Part 1 Study Design

Part 1 assessed the absolute bioavailability and evaluated the PK parameters of a single unlabelled oral dose and a radiolabelled intravenous (IV) microdose of capivasertib.

On Day 1, subjects received a single oral dose of 400 mg capivasertib (2 × 200 mg tablets), following a minimum 8 h overnight fast and no food until 4 h post-oral dose. Subjects then received an IV microdose of [^{14}C]AZD5363 (Capivasertib) solution (100 µg) containing not more than (NMT) 37.0 kBq ^{14}C, as a 15 min IV infusion, 1.25 h after the oral dose administration i.e. 15 min before the expected t_{max} (1.5 h) for the oral dose.

Subjects remained resident in the clinical unit until 96 h post-oral dose.

Blood samples were collected at regular intervals for PK and [^{14}C]AZD5363 (Capivasertib) analysis and safety from Day -1 to discharge from the clinical unit.

An evaluable subject in Part 1 was defined as a subject who had provided PK samples up to 72 h post-oral dose.

Part 2 Study Design

Part 2 was an assessment in the same healthy male subjects who completed Part 1.

Following a washout period of a minimum of 14 days, all subjects who participated in Part 1 of the study were to be admitted to the clinical unit for participation in Part 2 so that there would be least 6 subjects completing Part 2 of the study. However, one subject was withdrawn during the washout period due to 2 adverse events (AEs) of PPD, assessed as not related to investigational medicinal product (IMP), and therefore only 5 subjects were entered into Part 2 of the study. Subjects were admitted in the evening on the day prior to dosing (Day -1 of Part 2). On Day 1, subjects received a single dose of 400 mg [^{14}C]AZD5363 (Capivasertib) Oral Solution, containing NMT 4.8 MBq [^{14}C] following a minimum 8 h overnight fast and no food until 4 h post-dose, with the target being 4.3 MBq [^{14}C].

Subjects remained resident in the clinical unit until up to 168 h after dosing (up to Day 8).

It was planned that subjects were to be released as a group when all subjects had achieved a mass balance cumulative recovery of >90% or if <1% of the dose administered had been collected in urine and faeces within two separate, consecutive 24 h periods. Mass balance criteria had been met by all subjects by Day 8.

Blood samples were collected at regular intervals for PK and TR analysis, metabolite profiling and identification and safety from Day 1 to discharge from the clinical unit, as applicable. Urine and faeces were collected from Day 1 until up to Day 8 (see above for details).

A follow-up phone call took place between Day 15 and Day 19 to ensure the ongoing wellbeing of the subjects.

A subject in Part 2 was considered evaluable if they had provided mass balance and PK samples for 8 days after drug administration or had demonstrated >90% mass balance recovery, or had <1% of the administered dose eliminated in excreta for two consecutive days, whichever was sooner.

Number of Subjects (Planned and Analysed):

Planned: 8, Enrolled: 6, Completed: 5, Discontinued: 1.

Six subjects were included in the safety, PK and mass balance analysis sets for Part 1 and 5 subjects were included in the safety, PK and mass balance analysis sets for Part 2. One subject was withdrawn from the study prior to dosing in Part 2 due to an AE of syncope and was therefore not included in the PK and mass balance analysis sets for Part 2.

Diagnosis and Main Criteria for Inclusion:

Healthy, vasectomised male subjects between 30 and 65 years of age with a body mass index between 18.0 and 32.0 kg/m^2 and weight ≥50 kg and ≤100 kg as measured at screening.

Test Product, Dose and Mode of Administration, Batch Number:

In Parts 1 and 2 of the study, subjects received the following test IMPs:

Study Part	Regimen	IMP	Dose	Batch Numbers
1	A	Capivasertib film-coated tablet, 200 mg	400 mg (2 × 200 mg)	CCI (CCI relabelled batch)
	B	[^{14}C]AZD5363 (Capivasertib) Solution for Infusion 20 µg/mL (NMT 37.0 kBq/5 mL)[a]	100 µg; 5 mL	CCI CCI
2	C	[^{14}C]AZD5363 (Capivasertib) Oral Solution, 400 mg (NMT 4.8 MBq)	400 mg; 100 mL	CCI CCI

[a] IV infusion was administered 1.25 h after the oral dose administration i.e. 15 min before the expected t_{max} (1.5 h) for the oral dose.

The oral tablet was administered with a total of 240 mL of water. The oral solution was administered with water to achieve a total volume of 240 mL (including dosing volume and volume used to rinse the dosing vessel).

Reference Therapy, Dose and Mode of Administration, Batch Number:
Not applicable.

Duration of Treatment:
Subjects received a single oral dose of capivasertib followed by an IV microdose of [^{14}C]AZD5363 (Capivasertib) administered 1.25 h after the oral dose on one occasion in Part 1 and a single dose of [^{14}C]AZD5363 (Capivasertib) on one occasion in Part 2.

Criteria for Evaluation:

Mass Balance (Part 2 only)
The following mass balance parameters were calculated:

Parameter	Definition
$A_{e(urine)}$	Amount of TR excreted in urine
$F_{e(urine)}$	Amount of TR excreted in urine expressed as a percentage of the radioactive dose administered
$CumA_{e(urine)}$	Cumulative amount of TR excreted in urine
$CumF_{e(urine)}$	Cumulative amount of TR excreted in urine expressed as a percentage of the radioactive dose administered
$A_{e(faeces)}$	Amount of TR eliminated in faeces
$F_{e(faeces)}$	Amount of TR eliminated in faeces expressed as a percentage of the radioactive dose administered
$CumA_{e(faeces)}$	Cumulative amount of TR eliminated in faeces
$CumF_{e(faeces)}$	Cumulative amount of TR eliminated in faeces expressed as a percentage of the radioactive dose administered
$A_{e(total)}$	Amount of TR excreted in urine and faeces combined
$F_{e(total)}$	Amount of TR excreted in urine and faeces combined expressed as a percentage of the radioactive dose administered
$CumA_{e(total)}$	Cumulative amount of TR excreted in urine and faeces combined
$CumF_{e(total)}$	Cumulative amount of TR excreted in urine and faeces combined expressed as a percentage of the radioactive dose administered

Pharmacokinetics
The PK parameters for capivasertib (Parts 1 and 2) and [^{14}C]AZD5363 (capivasertib) (Part 1) in plasma and TR in plasma and whole blood (Part 2) were estimated where possible and appropriate for each subject by non-compartmental analysis methods using Phoenix® WinNonlin® software (v8.3, Certara USA, Inc., USA). The urine PK parameters for capivasertib were derived for each subject and collection interval in Part 2 using SAS.
The following Part 1 plasma PK parameters were calculated:

Parameter	Definition
t_{lag}	Time prior to the first measurable concentration after a single extravascular administration
t_{max}	Time of maximum observed concentration
C_{max}	Maximum observed concentration
AUC_{0-t}	Area under the curve (AUC) from time 0 to the time of last measurable concentration
AUC_{0-t}/D	AUC from time 0 to the time of last measurable concentration / dose level
AUC	AUC from time 0 extrapolated to infinity
AUC/D^a	AUC from time 0 extrapolated to infinity / dose level

Parameter	Definition
$AUC_{\%extr}$[b]	AUC from time of the last measurable concentration to infinity as a percentage of the AUC extrapolated to infinity
$t_{1/2}$	Terminal elimination half-life
λ_z	First order rate constant associated with the terminal (log-linear) portion of the curve
CL	Total body clearance calculated after a single IV administration
CL/F	Total body clearance calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown.
V_z	Volume of distribution based on the terminal phase calculated using AUC after a single IV administration
V_{ss}	Predicted volume of distribution at steady-state after single IV administration
V_z/F	Apparent volume of distribution based on the terminal phase calculated using AUC after a single extravascular administration where F (fraction of dose bioavailable) is unknown
MRT_{0-t}	Mean residence time from time 0 to time of the last measurable concentration
MRT	Mean residence time extrapolated to infinity
MAT	Mean absorption time of the unchanged drug in the systemic circulation
F	Absolute bioavailability based on AUC of oral formulation compared to IV adjusted for dose
lambda-z lower[b]	Lower limit on time for values to be included in the calculation of lambda-z
lambda-z upper[b]	Upper limit on time for values to be included in the calculation of lambda-z

[a] Dose corrections were applied on an individual basis to correct to a 1 mg dose.
[b] These values were listed but omitted from the descriptive statistics.

The following Part 2 plasma, whole blood and urine PK parameters were calculated:

Parameter	Definition
t_{lag}	Time prior to the first measurable concentration
t_{max}	Time of maximum observed concentration
C_{max}	Maximum observed concentration
AUC_{0-48}	AUC from time 0 to 48 h post-dose
AUC_{0-t}	AUC from time 0 to the time of last measurable concentration
AUC	AUC from time 0 extrapolated to infinity
$AUC_{\%extr}$[b]	AUC from time of the last measurable concentration to infinity as a percentage of the AUC extrapolated to infinity
$t_{1/2}$	Terminal elimination half-life
λ_z	First order rate constant associated with the terminal (log-linear) portion of the curve
CL/F	Total body clearance calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown.
CL_R	Renal clearance calculated using urine Ae/plasma AUC_{0-48}
V_z/F	Apparent volume of distribution based on the terminal phase calculated using AUC after a single extravascular administration where F (fraction of dose bioavailable) is unknown
MRT_{0-t}	Mean residence time from time 0 to time of the last measurable concentration
MRT	Mean residence time extrapolated to infinity
FE	fraction of drug systemically available that is excreted unchanged in the urine which is calculated as CL_R/CL
A_e[a]	amount of capivasertib excreted in urine

Parameter	Definition
F_e[a]	amount of capivasertib excreted in urine expressed as a percentage of the radioactive dose administered
lambda-z lower[b]	Lower limit on time for values to be included in the calculation of lambda-z
lambda-z upper[b]	Upper limit on time for values to be included in the calculation of lambda-z

[a] A_e and F_e were calculated as a discrete and cumulative parameter per time interval and over the entire sampling duration in SAS.
[b] These values were listed but omitted from the descriptive statistics.

TR blood to plasma concentration ratios were also determined for Part 2 only.

Metabolite Profiling and Identification

Metabolite profiling and identification is ongoing and will be performed on plasma, urine, and faeces samples by York Bioanalytical Solutions. These aspects are reported separately from this clinical study report as a standalone document.

Safety

The evaluation of safety parameters comprised analysis of AEs, laboratory variables (haematology, clinical chemistry and urinalysis), vital signs, electrocardiograms and physical examination findings.

Statistical Methods (Part 1 only):

Formal statistical analysis was performed on the PK parameter AUC/D only to assess the absolute bioavailability of capivasertib. The PK parameters underwent a natural logarithmic transformation and were analysed using mixed effect modelling techniques. The model included terms for treatment (i.e. regimen) fitted as a fixed effect and subject fitted as a random effect.

The adjusted means (LSmeans) including the differences from the pairwise comparisons and their associated 90% confidence intervals (CIs) obtained from the model were back transformed to the linear scale to obtain adjusted geometric mean ratios together with the 90% CIs of the ratios, where the ratio is defined as 400 mg capivasertib/100 µg IV [^{14}C]capivasertib.

Summary – Conclusions:

Pharmacokinetic Results

Pharmacokinetic Results: Part 1

The key geometric mean (geometric coefficient of variation [CV%]) plasma PK parameters following a single oral dose of 400 mg capivasertib are summarised below:

Parameter	capivasertib [N=6]
t_{lag}[a] (h)	0.000 (0.00-0.00)
t_{max}[a] (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)

Parameter	capivasertib [N=6]
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 (%)	28.55 (23.87, 34.15)[b]

[a] Median (range); [b] Value is geometric mean ratio (90% CI) from a linear mixed model based on AUC

Following a single oral dose of 400 mg of capivasertib, quantifiable plasma concentrations of capivasertib were evident from the first sampling time point of 0.25 h post-dose in all subjects. Median t_{max} occurred at 1.74 h post-dose (range: 0.75 h to 3.00 h post-dose).

Absolute bioavailability based on AUC of capivasertib following oral dosing was 29%. The inter-subject variability associated with AUC was moderate at 25.6%.

Terminal slopes were reliably determined for all 6 subjects and resultant elimination half-lives ranged between 11.5 h and 14.9 h. The geometric mean half-life was 12.9 h.

The key geometric mean (geometric CV%) plasma PK parameters following a single dose of 100 µg [^{14}C]AZD5363 (capivasertib) as a 15 min IV infusion are summarised below:

Parameter	[^{14}C]AZD5363 (capivasertib) [N=6]
t_{max}[a] (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)

Following 100 µg [^{14}C]AZD5363 (capivasertib) administered via a 15 min IV infusion, quantifiable concentrations of [^{14}C]AZD5363 (capivasertib) were observed in all subjects at the first sampling time point post-start of infusion (0.12 h). Median t_{max} occurred at 0.28 h post-start of infusion (range: 0.12 h and 0.33 h post-start of infusion).

Following C_{max}, concentrations showed a rapid distribution phase followed by an elimination phase. Terminal slopes were reliably determined for all 6 subjects and resultant apparent elimination half-lives ranged between 6.5 h and 7.5 h. The geometric mean half-life was 6.9 h. The inter-subject variability associated with peak and overall exposure was low at 21.8% and 15.0%, respectively.

The geometric mean (geometric CV%) volume of distribution and total clearance were approximately 378 L (17.9%) and 38.1 L/h (15.0%).

Pharmacokinetic Results: Part 2

The key geometric mean (geometric CV%) plasma and whole blood PK parameters following a single oral dose of 400 mg [^{14}C]AZD5363 (capivasertib) oral solution are summarised below:

Parameter	[^{14}C]AZD5363 (Capivasertib) Plasma	Total Radioactivity Plasma	Total Radioactivity Whole Blood
	N=5	N=5	N=5
t_{lag}[a] (h)	0.000 (0.00-0.00)	0.000 (0.00-0.00)	0.000 (0.00-0.00)
t_{max}[a] (h)	2.067 (1.37-3.00)	2.067 (1.50-3.00)	2.067 (2.00-4.00)
C_{max} (ng/mL)[c]	634 (10.2)	6840 (20.7)	4050 (36.7)
AUC_{0-48} (ng.h/mL)[c]	3330 (26.5)	NA	NA
AUC_{0-t} (ng h/mL)[c]	3400 (28.0)	36500 (33.9)	22800 (52.4)
AUC (ng.h/mL)[c]	3430 (27.8)	37700 (33.7)	33600 (13.6)
$T_{1/2}$ (h)	12.313 (24.2)	5.389 (31.2)	4.781 (4.2)
CL/F (L/h)	114 (27.5)	NA	NA
CL_R[b] (L/h)	8.30 (12.4)	NA	NA
V_z/F (L)	2030 (14.0)	NA	NA
$MRT_{(0-t)}$ (h)	8.910 (21.6)	NA	NA
MRT (h)	9.584 (20.3)	NA	NA
FE (%)	21.145 (12.9)	NA	NA

[a] Median (range), [b] Calculated over 0-48 h post dose, [c] Units for TR are 'ng equivalent', NA: not appliable

Following a single oral solution dose of 400 mg [^{14}C]AZD5363 (capivasertib), [^{14}C]AZD5363 (capivasertib) was rapidly absorbed with plasma concentrations quantifiable from the 0.25 h time point and median t_{max} observed at 2.07 h post-dose (range: 1.37 h to 3.00 h post-dose). The geometric mean plasma half-life of capivasertib

was 12.3 h, which was longer than that observed for plasma TR (5.4 h). However, it should be noted that a different analytical assay was used for each analyte, resulting in the capivasertib half-life being estimated over a later time interval (as results were still quantifiable up to 96 h) compared to the plasma TR (quantifiable up to 36 h). 7.4% of the capivasertib dose was excreted unchanged in the urine (Fe). The geometric mean renal clearance of capivasertib was 8.30 L/h. The fraction of capivasertib systemically available which was excreted in urine (FE) was 21.1%.

Exposure to capivasertib accounted for 9.1% of circulating plasma TR based on AUC.

The geometric mean whole blood to plasma TR concentration ratios indicated non-preferential distribution of TR to the cellular components of whole blood. There were no notable time-dependent differences in the ratios.

Mass Balance Results (Part 2 only)

Following a single oral dose of 400 mg [^{14}C]AZD5363 (capivasertib), a mean of 95.1% (range: 91.3% to 98.2%) of the total radioactivity administered was recovered by the end of the sampling period (168 h post-dose). 44.7% of the TR was recovered from urine and 50.4% of the total radioactivity was recovered from faeces.

Safety Results

Single doses of 400 mg oral capivasertib and 100 µg IV [14C]AZD5363 (capivasertib) in Part 1 and 400 mg oral [14C]AZD5363 (capivasertib) in Part 2 were generally found to be safe and well tolerated. No severe AEs, serious adverse events or deaths were reported in any study part.

In Part 1, 5 (83.3%) subjects reported a total of 6 AEs, 4 of which were considered to be possibly related to IMP. In Part 2, 4 (80.0%) subjects reported a total of 6 AEs, which were all considered to be possibly related to IMP.

All AEs were mild in severity, with the exception of 2 moderate AEs of PPD assessed as not related to IMP. All AEs resolved by the end of the study.

One subject was withdrawn due to the unrelated moderate AEs of PPD during the washout period between Part 1 and Part 2.

There were no clinically significant clinical laboratory tests, vital signs, electrocardiograms or physical examination findings.

Conclusions

Pharmacokinetic Conclusions: Part 1

Following IV administration of 100 µg [^{14}C]AZD5363 (capivasertib):

- The median t_{max} of [^{14}C]AZD5363 (capivasertib) was observed at 0.28 h post-start of infusion and was generally reached by the end of infusion.
- The geometric mean volume of distribution was 205 L.
- The geometric mean total clearance of [^{14}C]AZD5363 (capivasertib) was 38.1 L/h.
- The geometric mean apparent plasma half-life of [^{14}C]AZD5363 (capivasertib) was 6.9 h.

Following a single oral dose of 400 mg capivasertib tablet:

- The median t_{max} for capivasertib was 1.74 h post-dose.

- The absolute bioavailability of capivasertib following a 400 mg capivasertib oral dose was 29%.
- The geometric mean apparent terminal plasma half-life for capivasertib was 12.9 h. The half-life for the oral dose was estimated in a later time-interval than the half-life for the IV dose, likely due to the difference in assay sensitivity.

Pharmacokinetic and Mass Balance Conclusions: Part 2

Following a single oral dose of 400 mg [^{14}C]AZD5363 (capivasertib):

- An average of 95.1% of the radioactivity administered was recovered in excreta over the168 h sampling period.
- The mean total recovery of radioactivity from urine and faeces was 44.7% and 50.4%, respectively.
- The median t_{max} for capivasertib and plasma TR was 2.07 h.
- Exposure to capivasertib accounted for 9.1% of circulating plasma TR based on AUC.
- The geometric mean apparent terminal half-life was 5.4 h for plasma TR and 12.3 h for capivasertib.
- 7.4% of the dose and 21.1% of the systemically available capivasertib was excreted as unchanged drug in the urine and the geometric mean renal clearance of capivasertib was 8.30 L/h.
- The geometric mean whole blood to plasma TR concentration ratios ranged from 0.64 at 4 h to 0.85 at 24 h and there were no notable time-dependent differences in the ratios.

Safety

- Single doses of 400 mg oral capivasertib, 100 µg IV [^{14}C]AZD5363 (capivasertib) and 400 mg oral [^{14}C]AZD5363 (capivasertib) were generally found to be safe and well tolerated. Gastrointestinal disorders was the most common system organ class with observed AEs in this study (e.g. diarrhoea) which are expected AEs after capivasertib administration. The AE profile is in line with capivasertib Investigator's Brochure. No new safety concerns were raised for capivasertib.

Date of Report: 25 Nov 2022