Abbreviated Clinical Study Report Synopsis	
Drug Substance	Capivasertib
Study Code	D361FC00001
Edition Number	1
Date	08 March 2024
EudraCT Number	2021-000870-27
NCT Number	NCT05008055

A Modular Phase II, Open-Label, Multicentre Study to Assess the Efficacy and Safety of Capivasertib in Patients with Relapsed or Refractory B-cell Non-Hodgkin Lymphoma (CAPITAL)

Study dates:

First patient enrolled: 03 November 2021

Last patient last visit: Not applicable

The analyses presented in this report are based on a data cut-off on 22 August 2023

Date of early study termination: 13 June 2023. The development of capivasertib in haematologic malignancies was stopped. There were no safety issues in the study.

The analyses presented in this report are based on a clinical data lock date on 24 November 2023

Phase of development: Therapeutic exploratory (II)

International Co-ordinating Investigator:

PPD
PPD
PPD

Sponsor's Responsible Medical Officer:

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study Centres

Seventeen study centres (in 7 countries) screened patients and for 14 centres (in 6 countries) at least one patient was assigned to treatment.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Estimands

Objectives	Estimand Description
Primary	
• To estimate the effectiveness of the module-defined study treatment by assessment of ORR based on Lugano 2014 Classification response criteria in each Cohort as determined by BICR.	Objective response rate is defined as the proportion of patients achieving either CR or PR according to the Lugano 2014 Classification for NHL as assessed by BICR. The analysis included all patients included in the Response Evaluable Analysis Set. Data obtained from first dose up until progression, or the last evaluable assessment in the absence of progression, was included in the assessment of ORR, regardless of whether the patient withdrew from therapy. Patients who went off treatment without a response or progression, received a subsequent therapy, and then respond were not included as responders in the ORR. The measure of interest is the estimate of ORR. In addition, for sensitivity analysis purposes, ORR will be defined as the proportion of patients achieving either a CR or PR according to the Lugano 2014 Classification for NHL assessed by the investigator.
Secondary	
• To estimate the effectiveness of the module-defined study treatment by assessment of DoR based on Lugano 2014 Classification response criteria in each Cohort as determined by BICR.	Duration of response is defined as the time from the date of first documented response until date of documented progression according to the Lugano 2014 Classification for NHL as assessed by BICR, or death due to any cause. The analysis included all patients included in the Response Evaluable Analysis Set who had a response, regardless of whether the patient withdrew from therapy. The measure of interest is the median DoR. In addition, for sensitivity analysis purposes, DoR will be defined as the time from the date of first documented response until date of documented progression according to the Lugano 2014 Classification for NHL as assessed by the investigator.

Objectives	Estimand Description
• To estimate the effectiveness of the module-defined study treatment by assessment of PFS based on Lugano 2014 Classification response criteria in each Cohort as determined by BICR.	Progression-free survival is defined as the time from the date of first dose until documented disease progression according to the Lugano 2014 Classification for NHL as assessed by BICR, or death due to any cause. The analysis included all dosed patients, regardless of whether the patient withdrew from therapy, received another anti-lymphoma therapy, or clinically progressed prior to progression according to the Lugano 2014 Classification for NHL. The measure of interest is the median PFS. In addition, for sensitivity analysis purposes, PFS will be defined as the time from the date of first dose until progression according to the Lugano 2014 Classification for NHL as assessed by the investigator.
• To estimate the effectiveness of the module-defined study treatment by assessment of OS in each Cohort.	Overall survival is defined as time from the date of first dose until the date of death due to any cause. The analysis included all dosed patients, regardless of whether the patient withdrew from therapy or received another anti-lymphoma therapy. The measure of interest is the median OS.
• To assess patient-reported disease-related symptoms, functioning and health-related quality of life of the module-defined study treatment in each Cohort. [a]	Patient-reported disease-related symptoms, functioning and health-related quality of life as measured by EORTC QLQ-C30. The analysis included all dosed patients and was to be summarised descriptively. The measures of interest are mean and mean change from baseline in each of the functional scales, symptom scales, and global health status/quality of life scores at each timepoint.
• To assess patient-reported symptomatic AEs/tolerability of module-defined study treatment in each Cohort. [a]	Patient-reported symptomatic AEs and overall side effect burden as measured by PGI-TT and selected items from PRO-CTCAE. The analysis included all dosed patients and was to be summarised descriptively. The measures of interest will be proportion of patients reporting different levels of each symptomatic AEs and proportion of patients reporting different levels of overall side effect burden at each timepoint.
• To estimate the effectiveness of the module-defined study treatment by assessment of TFST in each Cohort. [a]	TFST is defined as time from date of first dose until the start date of first subsequent anti lymphoma therapy after discontinuation of study treatment or death due to any cause. The analysis was to include all dosed patients regardless of whether the patient withdrew from therapy, received

Objectives	Estimand Description
	another anti-lymphoma therapy or clinically progressed prior to progression according to the Lugano 2014 Classification for NHL. The measure of interest is the median TFST.
• To estimate the effectiveness of the module-defined study treatment by assessment of TTR in each Cohort. [a]	TTR is defined as time from date of first dose until the date of first documented objective response per the Lugano 2014 Classification for NHL as assessed by BICR. The analysis was to include all patients included in the Response Evaluable Analysis Set who had a response regardless of whether the patient withdrew from therapy. The measure of interest is the median of TTR.
Safety	
• To assess safety and tolerability of the module-defined study treatment in each Cohort.	Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory, and ECGs. Assessments related to AEs cover: • Occurrence/frequency • Relationship to the module-defined study treatment as assessed by investigator • CTCAE grade • Seriousness • Death • AEs leading to discontinuation of the module-defined study treatment • AESIs • Other significant AEs The analysis included all dosed patients and will be summarised descriptively.
Pharmacokinetics	
• To determine the PK of capivasertib when administered in patients in each Cohort.	Plasma concentration of capivasertib pre-dose (Ctrough) and post-dose (eg, 1 h, 2 h and 4 h). Plasma PK parameters derived from a population PK model, as permitted by the data.

Exploratory objectives and endpoints are included in the clinical study report body.

[a] These objectives were not fully analysed.

AE = adverse event; AESI = adverse event of special interest; BICR = blinded independent central review; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DoR = duration of response; ECG = electrocardiogram; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; NHL = Non-Hodgkin lymphoma; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PGI-TT = Patient Global Impression of Treatment Tolerability; PK = pharmacokinetics; PR = partial response; PRO-CTCAE = Patient-reported Outcomes-Common Terminology Criteria for Adverse Events; TFST = time to first subsequent therapy or death; TTR = Time to objective response.

Study Design

This study was an open-label, multicentre Phase II study of capivasertib administered orally in patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (NHL). The structure of the protocol followed a modular design. Patients were to be enrolled concurrently in the individual Cohorts according to the type of NHL. Only Module 1 was started.

Module 1 (capivasertib monotherapy) included 3 Cohorts:

- Cohort 1A: capivasertib monotherapy in patients with R/R follicular lymphoma (FL).
- Cohort 1B: capivasertib monotherapy in patients with R/R marginal zone lymphoma (MZL).
- Cohort 1C: capivasertib monotherapy in patients with R/R mantle cell lymphoma (MCL).

On 13 June 2023, AstraZeneca decided to stop enrolment into the study and stop the development of capivasertib in haematologic malignancies. There were no safety concerns related to the study.

Target Population and Sample Size

The study included male and female patients aged ≥ 18 years of age with a life expectancy of > 6 months and an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. For inclusion in Module 1 patients had to have bi-dimensionally measurable disease on cross-sectional imaging by computed tomography or magnetic resonance imaging with at least one nodal lesion > 1.5 cm in the long axis or at least one extranodal lesion > 1 cm in long axis. The following histologically confirmed diagnoses were required for the 3 Cohorts:

- Cohort 1A (R/R FL): Diagnosis of FL Grade 1, 2, or 3a, as assessed by investigator or local pathologist.
- Cohort 1B (R/R MZL): MZL including splenic, nodal, and extranodal subtypes, as assessed by investigator or local pathologist.
- Cohort 1C (R/R MCL): MCL, with documentation of monoclonal B cells that had a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1, as assessed by investigator or local pathologist.

The hypotheses for analysis of the primary efficacy endpoint objective response rate (ORR) were based on a planned sample size of 272 patients (94, 94, 84 in Cohorts 1A, 1B, and 1C, respectively). Due to the early termination of the study, 30 patients were assigned (16, 4, 10 in Cohorts 1A, 1B, and 1C, respectively).

Investigational Product: Dosage, Mode of Administration and Batch Numbers

Intervention name	Capivasertib (AZD5363)		
Type	Drug		
Dose formulation	Tablet		
Unit dose strength(s)	CCI mg	CCI mg	
Dosage level(s)	Starting dose: 480 mg (CCI mg) BD	Reduced dose 1: CCI mg (CCI mg) BD	Reduced dose 2: CCI mg (CCI mg) BD
	Given as an intermittent schedule: Days 1 to 4 in each week of a 28-day treatment cycle, depending on tolerability. Morning and evening doses taken approximately 12 ± 2 hours apart (at the same hour of the day).		
Route of administration	Oral		
Use	Experimental		
IMP and NIMP	IMP		
Sourcing	Supplied by AstraZeneca		
Packaging and labelling	Study treatment was provided in white high-density polythene bottles. Each bottle was labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement.		
Batch/lot number(s)	CCI CCI		

BD = twice daily; IMP = investigational medicinal product; NIMP = non-investigational medicinal product.

Duration of Treatment

Capivasertib was taken at 480 mg orally twice daily 4 days on/3 days off until disease progression unless there was evidence of unacceptable toxicity or if the patient/investigator requested to stop the treatment.

Statistical Methods

Primary Efficacy Endpoint, ORR

ORR was defined as the proportion of patients achieving either complete response (CR) or partial response (PR) as best response as assessed by blinded independent central review (BICR). In addition, for sensitivity analysis purposes, ORR was defined as the proportion of patients achieving either CR or PR as assessed by the investigator. Both analyses were based on the Response Evaluable Analysis Set.

The analysis of ORR was performed according to the Lugano 2014 Classification for NHL as assessed by BICR.

Summaries were produced to present the number and percentage of patients with a response (CR/PR) based upon the number of patients with measurable disease at baseline per BICR. ORR was calculated and binomial exact confidence intervals (CIs) at 95% were presented for patients in the Response Evaluable Analysis Set.

A summary showing concordance between BICR and investigator's assessments is presented. The concordance rate was the number of patients that are concordant over the total number of patients assessed. The patients are concordant when the investigator and BICR concluded the same response assessment for a patient.

Best Objective Response (BoR)

BoR was calculated based on the overall visit responses recorded in the BICR dataset. It was the best response a patient had following enrolment, but prior to starting any subsequent anti-lymphoma therapy and up to and including Lugano progression or the latest evaluable assessment in the absence of Lugano progression. BoR is summarised by number of patients and percentage for each category (CR, PR, stable disease, progression of disease, and not evaluable), with no formal statistical analysis presented.

Secondary Efficacy Endpoint, Duration of Response (DoR)

The analysis was based on BICR reviewed data. Sensitivity analyses were performed based on investigator assessments.

DoR was defined as the time from the date of first documented response until the date of documented progression or death due to any cause in the absence of disease progression. The end of response should have coincided with the date of progression or death from any cause used for the progression-free survival endpoint. The time of the initial response was defined as the latest of the dates contributing towards the first visit that was CR or PR.

Kaplan-Meier plots of DoR are presented. Median DoR, including 95% CIs, are also presented, calculated from the Kaplan-Meier curve. In addition, the number of patients still responding at 3, 6, and 12 months after initial response are presented. Swimmer plots that show the profile of each patient who responded are also presented.

Safety Analysis

All safety summaries and analyses were based upon the Safety Analysis Set and presented either by Cohort and overall, or by Cohort alone.

Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities Version 26.0 and were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Summary tables for AEs include treatment-emergent AEs only. Adverse events of special interest (AESIs), events of scientific and medical interest specific to

the further understanding of the capivasertib safety profile, were closely monitored and investigators were expected to communicate any AESIs to AstraZeneca urgently.

Clinical chemistry, haematology, vital signs, ECOG performance status, and echocardiogram data are listed individually by patient and appropriately summarised. For all laboratory values that were included in the CTCAE, the CTCAE Grade was calculated.

The electrocardiogram (ECG) parameters obtained from the central review are summarised over time in terms of absolute values and change from baseline. QT Interval corrected using Fridericia's formula outliers (defined as values following study treatment that are greater than 450 ms or increases from baseline greater than 30 ms) are summarised using cumulative counts and percentages.

Pharmacokinetic (PK) Analysis

The PK analyses were based upon the PK Analysis Set and exclusion of data are documented and justified. Plasma concentrations of capivasertib are listed by patient and timepoint. Plasma concentrations are summarised by Cohort and scheduled timepoint using descriptive statistics.

Study Population

A total of 42 patients were enrolled/screened up to the data cut-off on 22 August 2023. Twelve patients were screen failures, and the main reason for screen failure was due to the exclusion criteria related to inadequate bone marrow reserve or organ function (4 patients). In total 30 patients were assigned and all started treatment. A total of 25 (83.3%) patients discontinued treatment and the main reason was objective disease progression.

Summary of Efficacy Results

The number of patients achieving an objective response was low across all Cohorts (3 [18.8%], 1 [33.3%], and 3 [30.0%], in Cohorts 1A, 1B, and 1C, respectively). For all Cohorts the sample size was limited, and a high number of patients had a BoR of not evaluable for the BICR assessments.

DoR was lower than expected (the median time to onset of response from first dose was 2.0 months and the median DoR was 1.9 months), confounded by the small number of patients achieving objective response.

Summary of Pharmacokinetic Results

The observed plasma concentrations of capivasertib in this study were comparable to the other studies in adults. In Cohort 1A (N = 16), maximum observed drug concentration (Cmax) was seen at Cycle 1 Day 1 at 2 hours post-dose with a geometric mean value of 883.7 ng/mL and lowest observed drug concentration reached before the next dose was administered (Ctrough) at Cycle 1 Days 8, 15 and 22 were 6.149, 5.844, and 7.974 ng/mL, respectively. In Cohort 1B,

(N = 4), Cmax was observed at Cycle 1 Day 1 at 2 hours post-dose with a geometric mean value of 962.9 ng/mL and Ctrough at Cycle 1 Days 8 and 15 were 8.477 and 9.245 ng/mL, respectively. In Cohort 1C (N = 9), Cmax was observed at Cycle 1 Day 1 at 2 hours post-dose with a geometric mean value of 976.1 ng/mL and Ctrough at Cycle 1 Days 8 and 15 were 14.31 and 32.36 ng/mL, respectively.

Summary of Safety Results

- Whilst most patients experienced at least one AE (29 [96.7%] patients) and the majority of these were considered possibly related to study treatment by the investigator (25 [83.3%] patients), the most frequently reported AEs (> 10% patients) were as expected for capivasertib treatment in this study population:
  - Diarrhoea (21 [70.0%] patients), Nausea (9 [30.0%] patients), Rash, Fatigue (5 [16.7%] patients each), and Decreased Appetite, Headache, Vomiting, Pyrexia (4 [13.3%] patients each).
- A total of 15 (50.0%) patients reported AEs of CTCAE Grade 3 or higher, and 9 (30.0%) patients reported AEs of CTCAE Grade 3 or higher, assessed by investigator as possibly related to study treatment. Possibly related AEs of CTCAE Grade 3 or higher were reported by more than one patient for Diarrhoea (3 [10.0%] patients) and Rash (2 [6.7%] patients).
- A total of 5 (16.7%) patients experienced at least one SAE and for 3 (10.0%) patients these SAEs were assessed by the investigator as possibly related to study treatment (one patient Perirectal abscess and Hyperglycaemia, one patient Diarrhoea, and one patient Erythema multiforme).
- No patient had an AE with outcome of death (3 patients died due to disease under investigation).
- A total of 3 (10.0%) patients had an AE that led to discontinuation of treatment.
- A total of 26 (86.7%) patients experienced at least one AESI and the most frequently reported AESIs were Diarrhoea (21 [70.0%] patients) and Rash (5 [16.7%] patients).
- There were no clinically important trends or changes from baseline for clinical laboratory parameters, vital signs, and ECG results.

Conclusions

- ORR and DoR, assessed by BICR, were lower than expected. However, the sample size was considerably smaller than planned and therefore the results should be interpreted with caution.
- The observed plasma concentrations of capivasertib in this study were comparable to the other studies in adults, with mean Cmax values ranging between 883.7 to 976.1 ng/mL and mean Ctrough values ranging between 5.84 to 32.36 ng/mL.
- Treatment with oral capivasertib monotherapy was well tolerated, and no new safety concerns were identified.