Clinical Study Protocol	
Study Intervention	Capivasertib
Study Code	D361FC00001
Version	6.0
Date	24 Feb 2022

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)

Sponsor Name:

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This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number:

Amendment Number: 03

Study Intervention:
Capivasertib (AZD5363)
Study Phase: II

Short Title:

A Phase II trial of capivasertib in R/R B-cell NHL.

Acronym:

CAPITAL

Study Physician Name and Contact Information will be provided separately

International co-ordinating investigators

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 03 (v6.0)	24 February 2022
Amendment 02 (v3.0)	28 July 2021
Amendment 01 (v2.0)	28 April 2021
Original Protocol (v1.0)	18 February 2021

The summary of changes for Amendment 03 is provided below. Refer to Appendix M for a summary of the previous amendments.

Previous numbering inadvertently did not follow global/local versioning guidance, hence global amendment 03 is named v6.0 (v4.0 was used for local Korea amendment and v5.0 was used for local UK amendment).

Amendment 03, v6.0 [24 February 2022]

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This protocol amendment incorporates changes made for local protocol amendments applicable in the United Kingdom and South Korea that were prepared in response to queries from the Medicines and Healthcare Products Regulatory Agency (MHRA) and the South Korean Ministry of Food and Drug Safety (MFDS), respectively. In addition, to implement updates based on updated capivasertib safety requirements (non-substantial, based on routine AZ safety data review), modification of Module 1-specific eligibility criteria in agreement with the Study Steering Committee (SSC) to allow a greater number of patients to potentially benefit from capivasertib monotherapy, revision of time windows for some study procedures and for template and other updates to aid sense and flow of the document.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
CORE			
Section 2.3.1 (Risk Assessment, Table 1)	Addition of erythema multiforme to identified risks for capivasertib.	As part of AstraZeneca's routine safety surveillance process and ongoing review of the clinical trial safety data, erythema multiforme has been identified as an identified risk for capivasertib.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 5.1 (Core Inclusion Criteria 5 and 7) & Section 5.3.4 (Pregnancy and Contraception)	Clarification on contraception methods considered as highly effective for both male and female patients.	Amended in line with MHRA request.	Substantial
Section 5.1 (Core Inclusion Criteria 6)	Addition of serum for pregnancy test.	Clarification that pregnancy test should be on serum.	Substantial
Section 5.2 (Core Exclusion Criteria)	Exclusion criteria 6d: Current criterion states that ALT and AST must be > 2.5 × ULN; Amended to clarify that ALT *or* AST can fulfil the criterion.	Amended to 'or' for consistency within the document.	Substantial
	Exclusion criteria 6e: Amended to clarify the bilirubin criteria for patients (ie, > 3 × ULN) with documented Gilbert's syndrome.	Amended in line with MHRA request.	Substantial
	Exclusion criteria 12 c): Criteria has been updated to exclude "Strong inhibitors or inducers of CYP3A4 within 2 weeks prior to the first dose of study treatment (3 weeks for St John's wort), or drugs that are sensitive to inhibition of CYP3A4 within 1 week prior to the first dose of study treatment."	Updated for clarity; removed restrictions for CYP2D6 and CYP2C9 substrates based on physiologically-based PK modelling; added MATE1 and OCT2 transporter substrates under the appendix of drugs that may be influenced by capivasertib.	Substantial
Section 6.5.1 (Drugs that Prolong QT Interval)	Text has been added describing management of concomitant	In order to keep the most up-to-dated list of drugs known to or potentially prolonging the QT intervals, reference to https://www.crediblemeds.org/	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	medications that prolong QT interval.	is made rather than referring to the list detailed in the study protocol. Therefore, this section has been added while the respective reference in Appendix F1 has been removed.	
Section 7.3 (Lost to Follow-up)	Deletion of text regarding independent third party.	Third party vendors for the collection of vital status are not used in this study.	Non-substantial
Section 8 (Study Assessments and Procedures - CORE)	Addition of text regarding bone marrow aspirates/biopsy performed as part of standard of care and up to 12 weeks prior to ICF signature.	To avoid unnecessary repetition of invasive procedures (ie, BM biopsy) unless clinically indicated by the investigator.	Substantial
	Addition of text regarding imaging assessments performed as part of standard of care and up to 5 weeks prior to ICF signature.	To avoid patients to be exposed to unnecessary radiation by repeating PET/CT assessment unless clinically indicated.	Substantial
Section 8.1.1 (Bone Marrow Assessments)	Deletion of text describing uses of baseline bone marrow aspirate/biopsy for confirmation of disease status/profiling.	Updated for clarity as central histological disease confirmation is not required in this study.	Non-substantial
	Increase from 14 days to 28 days for bone marrow biopsy/aspirate assessment after respective radiological assessment.	Window for bone marrow/biopsy assessments increased to 28 days in alignment with routine clinical practice and to allow more time for the site to plan the assessments after the radiological evaluation.	Substantial
Section 8.1.2 (Imaging Assessments)	Amended to allow contrast enhanced CT to be performed before PET if the time	Clarification to allow contrast enhanced CT to be performed before PET with sufficient	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	between them is more than 6 hours.	time between to prevent interference in the PET scan.	
Section 8.1.4.1 (Endoscopy)	Addition of 28-day period for assessment after respective radiological assessment.	Window for endoscopy increased to 28 days in alignment with routine clinical practice and to allow more time for the site to plan the assessments after the radiological evaluation.	Substantial
Section 8.2.4 (Clinical Safety Laboratory Assessments) & Section 10.1.1 (Schedule of Activities – Capivasertib Monotherapy)	CCI [redacted]	CCI [redacted]	Non-substantial
	Text ..patients with positive serology for HBV or HCV..' has been amended to '…patients with positive anti HBcAb or anti-hepatitis C Ab at screening…'	Updated for clarity and consistency with eligibility criteria.	Non-substantial
Section 8.2.4 (Clinical Safety Laboratory Assessments, Table 4)	Table 4 footnote added for urine microscopy "Denmark only: U-Microscopy is not required".	Clarification added since it is no longer a national standard.	Substantial
	Addition of gamma-glutamyl transferase to the laboratory safety variables	Amended in line with updated safety requirements and to ensure comprehensive assessment on liver function.	Substantial
Section 8.3.11.1 (Maternal Exposure) and Section 8.3.12.1 (Paternal Exposure)	Congenital abnormality(/ies) changed to congenital anomaly(/ies)/birth defect(s).	Updated in line with current template text.	Non-substantial
Section 8.3.13 (Adverse Events of Special Interest)	Removal of urinary tract infection, pneumonia, and Torsades de pointes from the AESI list. Addition of infective pneumonia.	Updated in line with current list of AESIs for capivasertib. Following routine safety data review at the program level, these terms were found to no longer meet AESI criteria as defined by internal processes	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
		including, but not limited to, risks for which some sort of action is required (eg, additional data collection or risk mitigation strategy).	
Section 8.6.1 CCI [redacted]	CCI [redacted]	CCI [redacted]	Substantial
Section 9.4.2.2 (Secondary Endpoints)	Addition of text for DoR confirming the use of the same censoring rules as applied for PFS.	Clarification of censoring process.	Non-substantial
Throughout	Minor administrative changes.	Revisions made to correct errors in format, typography, or language.	Non-substantial
MODULE 1 (Section 10): Capivasertib Monotherapy in Patients with Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma			
Section 10.1.1 (Schedule of Activities – Capivasertib Monotherapy, Table 6 and Table 7)	Clarified that HbA1C and lipids should be monitored starting from C1D1.	Updated for clarity.	Non-substantial
	Addition of vital signs assessment at 30 days after last dose follow-up.	Amended in line with safety requirements.	Substantial
	ECHO/MUGA changed from as clinically indicated to at end of therapy and as clinically indicated	Amended in line with safety requirements and to ensure cardiac function is evaluated also at the end of treatment.	Substantial
	Addition of new footnote k (Table 6) to clarify that the post-dose glucose sample can be collected under	As no significant differences in plasma glucose profiles were observed following capivasertib tablet dosing in the fed, partially fasted and	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	fasting or non-fasting conditions.	fasted status, this clarification avoid unnecessary fasting for patients.	
	Deletion of Lugano response assessment at screening.	Evaluation of disease response is only required during study drug treatment and therefore is not applicable at screening.	Non-substantial
	Addition of new footnotes to delineate central laboratory from local laboratory.	Updated for clarity.	Non-substantial
	Addition of time windows for PK sampling.	Updated for clarity to ensure standardization in timing of PK sampling.	Non-substantial
	Serum glucose sampling after C2D1 is pre-dose only.	Updated for clarity.	Non-substantial
Section 13.1.1 (Additional Inclusion Criteria for Cohort 1A [R/R FL])	Deletion of text for inclusion criteria 4 stating the maximum number of prior lines of therapy.	To allow a greater proportion of patients to be enrolled as endorsed by the Study Steering Committee (SSC).	Substantial
Section 13.1.2 (Additional Inclusion Criteria for Cohort 1B [R/R MZL])	Deletion of text for inclusion criteria 4 stating the maximum number of prior lines of therapy.	To allow a greater proportion of patients to be enrolled as endorsed by the SSC.	Substantial
Section 13.1.3 (Additional Inclusion Criteria for Cohort 1C [R/R MCL])	Deletion of text for inclusion criteria 3 stating the maximum number of prior lines of therapy.	To allow a greater proportion of patients to be enrolled as endorsed by the SSC.	Substantial
	South Korea Only: MCL patients must not have another available beneficial treatment option.	Updated in line with MFDS request.	Non-substantial
Section 13.2 (Exclusion Criteria)	Deletion of text for exclusion criteria 3 for blastoid or pleiomorphic variant	To allow a greater proportion of patients to be enrolled as endorsed by the SSC.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	or documented TP53 mutation.		
Section 15.1 (Discontinuation of Study Intervention)	In the event a criterion is met to stop or pause the study recruitment in Module 1, the study will only restart after submission and approval of a substantial amendment by the regulatory authority and IRB/IEC.	Amended in line with MHRA request.	Substantial
Appendix B2 (Definition of Serious Adverse Events)	Congenital abnormality changed to congenital anomaly.	Updated in line with current template text.	Non-substantial
Appendix F (Guidance Regarding Potential Interactions of Capivasertib with Concomitant Medications)	Appendix has been updated with current text from updated safety requirements.	Updated for clarity; removed restrictions for CYP2D6 and CYP2C9 substrates based on physiologically-based PK modelling; added MATE1 and OCT2 transporter substrates under the appendix of drugs that may be influenced by capivasertib.	Substantial
Appendix M (Protocol Amendment History)	Addition of this appendix.	Included as per template guidance.	Non-substantial
Throughout	Minor administrative changes.	Revisions made to correct errors in format, typography, or language.	Non-substantial

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

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)

Short Title:

A Phase II trial of capivasertib in R/R B-cell NHL.

Rationale:

Refer to the relevant Module for details.

Objectives and Endpoints:

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 will include 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, will be included in the assessment of ORR, regardless of whether the patient withdraws from therapy. Patients who go off treatment without a response or progression, receive a subsequent therapy, and then respond will not be 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.

Objectives	Estimand description
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 will include all patients included in the response evaluable analysis set who had a response, regardless of whether the patient withdraws 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.
• 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 will include all dosed patients, regardless of whether the patient withdraws from therapy, receives another anti-lymphoma therapy, or clinically progresses 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 the time from the date of first dose until the date of death due to any cause. The analysis will include all dosed patients, regardless of whether the patient withdraws from therapy or receives another anti-lymphoma therapy. The measure of interest is the median OS.

Objectives	Estimand description
• To assess patient-reported disease-related symptoms, functioning and health-related quality of life of the module-defined study treatment in each cohort	Patient-reported disease-related symptoms, functioning and health-related quality of life as measured by EORTC QLQ-C30. The analysis will include all dosed patients and will 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 time point.
• To assess patient-reported symptomatic AEs/tolerability of module-defined study treatment in each cohort	Patient-reported symptomatic AEs and overall side effect burden as measured by PGI-TT and selected items from PRO-CTCAE. The analysis will include all dosed patients and will be summarised descriptively. The measures of interest will proportion of patients reporting different levels of each symptomatic AEs and proportion of patients reporting different levels of overall side effect burden at each time point.
• To estimate the effectiveness of module-defined study treatment by assessment of TFST in each cohort	Time to first subsequent therapy or death 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 will include all dosed patients, regardless of whether the patient withdraws from therapy, receives another anti-lymphoma therapy or clinically progresses prior to progression according to the Lugano 2014 Classification for NHL. The measure of interest is the median TFST.
• To estimate the effectiveness of module-defined study treatment by assessment of TTR in each cohort	Time to objective response 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 will include all patients included in the response evaluable analysis set who had a response regardless of whether the patient withdraws from therapy. The measure of interest is the median of TTR.

Objectives	Estimand description
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 module-defined study treatment • AESIs • Other significant AEs The analysis will include 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.

AE: adverse event; AESI: adverse event of special interest; BICR: blinded independent central review; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; Ctrough: observed lowest drug concentration reached before the next dose is administered; 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.

For exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design:

This study is an open-label, multicentre Phase II study of capivasertib administered orally in patients with relapsed or refractory (R/R) B-cell non-Hodgkin's lymphoma (NHL) (Section 1.2). The structure of the protocol follows a modular design. Patients will be enrolled concurrently in the individual cohorts according to the type of NHL.

This is a non-randomised study. Each patient approved for screening is assigned a unique participant enrolment number. If a patient withdraws from the study, then the enrolment

number cannot be reused. Study treatment will be dispensed or administered, as applicable, at the study visits summarised in the SoA in the relevant Module.

The study may include module-specific interim analyses. These interim analyses will be assessed against a decision framework (Frewer et al 2016). Based on the interim results, study enrolment could pause and the sponsor may opt to amend the protocol to adjust the dosing schedule based on emerging data, permanently close the specific cohort, or add in a new cohort for testing capivasertib in combination with other agents in that population which would be detailed in an amendment.

Disclosure Statement:

This is a non-randomised, open-label, modular study with no masking.

Number of Participants:

Refer to the relevant Module for details.

Intervention Groups and Duration:

Refer to the relevant Module for details.

Data Monitoring Committee:

This study will have a Study Steering Committee (SSC). The details of the roles and responsibilities of the SSC are provided in a charter separate from the Core Protocol. A Safety Review Committee may be established in case a module evaluating capivasertib in combination with other agents is added in the future.

Statistical Methods

Analyses will be performed by AstraZeneca or its representatives, including contract research organisations (CROs). A comprehensive statistical analysis plan (SAP) will be developed and will describe the patient populations to be included in the analyses, the analyses including any subgroup analyses or sensitivity analyses, and the procedures to account for missing, unused, and spurious data.

Each Cohort will be analysed separately.

The analysis of objective response rate (ORR) will be performed according to the Lugano 2014 Classification for NHL (Cheson et al 2014) as assessed by blinded independent central review (BICR). Objective response rate will be defined as response of CR or PR.

The efficacy endpoints for tumour response (ORR, duration of response [DoR] and time to objective response [TTR]) will be summarised and analysed based on the response evaluable analysis set. The efficacy endpoints for overall survival (OS), progression-free survival (PFS),

time to first subsequent therapy or death (TFST), and quality of life (QoL) will be summarised based on the safety analysis set. Safety and treatment exposure data will be summarised based on the safety analysis set.

Continuous data will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Geometric mean and coefficient of variation may be presented as applicable. Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated from the population total. Time to event variables will be presented using the Kaplan-Meier methodology, including median time calculated from the Kaplan-Meier curves.

Interim analyses will be further detailed in the relevant Module.

The primary analysis for each cohort will be conducted after all patients treated with capivasertib have had the opportunity to be treated for 6 months.

The data cut-off for the final analysis for each cohort will occur approximately 18 months after the last patient treated with capivasertib has been enrolled in the cohort or when 70% of patients have progressed or died (due to any reason) in the cohort, whichever occurs first.

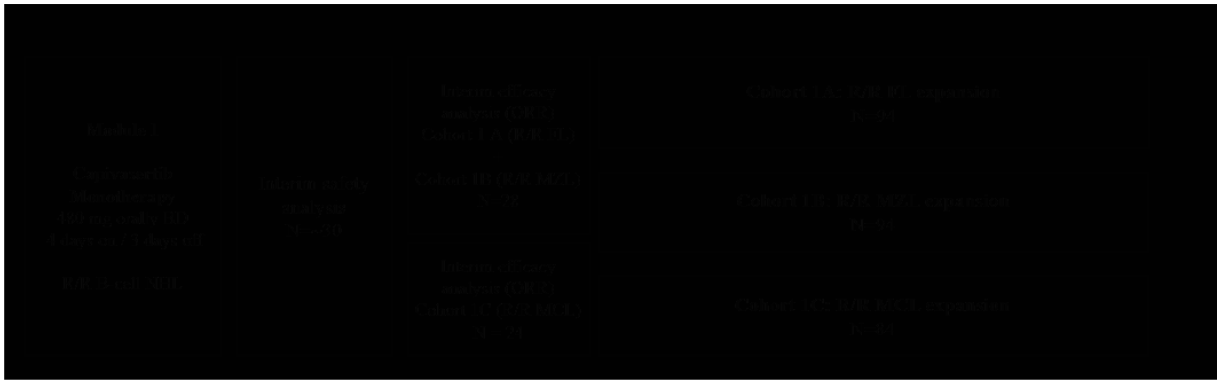
Additional OS follow-up analyses for each cohort may be performed after the final analysis, until 70% of the patients treated with capivasertib have died due to any cause.

Additional data cuts may also be performed, if required.

1.2 Schema

This study will be conducted in independent Modules. Study design is presented in Figure 1.

Figure 1 Study Design



BD: twice a day; FL: follicular lymphoma; MCL: mantle cell lymphoma; MZL: marginal zone lymphoma; NHL: non-Hodgkin lymphoma; ORR: objective response rate; R/R: relapsed or refractory.

Subsequent Modules may be further added via formal protocol amendments based on emerging supportive preclinical and clinical data and study rationale.

1.3 Schedule of Activities

Refer to individual schedule of assessments (SoA) for the relevant Module.

2 INTRODUCTION - CORE

This is a modular, Phase II study of capivasertib in patients with R/R B-cell NHL. The structure of the CSP also follows a modular design with the protocol, hereafter referred to as the 'Core Protocol', presenting study information applicable to all patients in this study, and 'Modules' presenting only module-specific information.

2.1 Study Rationale

Non-Hodgkin lymphoma is the 7th most common cancer in the US and represents 4.3% of all new cancer cases in the US. In 2020, it is estimated that there will be 77,420 new cases of NHL, with a median age at diagnosis of 67 years, and an estimated 19,940 deaths related to this disease (Howlader et al 2020).

AKT is a node of multiple signalling pathways promoting tumorigenesis, inhibiting apoptosis, impacting the cell cycle, and promoting invasion and migration. Capivasertib (AZD5363) is a potent, selective inhibitor of the kinase activity of all 3 isoforms of AKT (AKT1, AKT2, and AKT3) that is administered orally on an intermittent schedule of administration. An estimated 900 patients with solid tumours have received capivasertib in AstraZeneca sponsored studies, as monotherapy or in combination with other anti-cancer agents (refer to the current capivasertib IB) showing a manageable safety profile and promising efficacy data.

Capivasertib is targeting a different node on the PI3K-AKT-TOR signalling pathway to the established PI3K inhibitors that have proven efficacy in lymphoma (and currently approved for R/R FL) and has shown already promising efficacy data in solid tumours.

Limited preclinical models are available for studying the effect of capivasertib in indolent lymphoma either in vitro or in vivo. In an extended cell panel, capivasertib monotherapy demonstrated in vitro activity in lymphoma lines representative of MCL and DLBCL at a concentration less than 1 µM (Lynch et al 2016). In vitro, capivasertib monotherapy shows variable inhibition of MCL cell line growth. It shows 100% tumour growth inhibition in 2 out of 7 MCL cell lines (Granta-519, JVM-2) at 3 µM and 50% inhibition in a further 3 cell lines at 3 µM (Mino, Jeko, Z-138). In addition, capivasertib shows greater than 30% tumour growth inhibition in 2 MCL line models in vivo (data on file).

For these reasons, capivasertib may represent a novel attractive therapeutic option for the treatment of patients with haematological malignancies.

2.2 Background

2.2.1 Role of AKT Inhibition in B-cell Lymphoid Malignancies

The PI3K/AKT/PTEN pathway is frequently deregulated in cancers and drives tumour growth and cell survival. All 3 AKT isoforms are activated in types of solid tumours (breast, prostate,

ovarian, pancreatic, gastric cancers) and in haematological malignancies. This activation is often associated with resistance to established cancer therapies as well as advanced disease and/or poor prognosis. AKT activation in tumours is largely due to input from other signalling pathways upstream of AKT (eg, mutation of oncogenes such as Ras, Bcr-abl, mutation of receptor tyrosine kinases such as epithelial growth factor receptor, amplification of HER2, loss of PTEN function, and mutations of PI3K).

Inhibition of PI3K, AKT or mTOR kinases have been shown to confer anti-proliferative effect and apoptosis in a variety of lymphoma types in vitro (Georgakis and Younes 2006; Jia et al 2008; Yuan and Cantley 2008; Engelman 2009). Several PI3K inhibitors (ie, idelalisib, duvelisib, copanlisib) have been already approved for the treatment of R/R FL (ZYDELIG USPI; COPIKTRA USPI; ALIQOPA USPI).

Phosphorylation of AKT represents PI3K pathway activation, and is common in lymphomas. Hodgkin lymphoma commonly demonstrates AKT phosphorylation in cell lines and in 63% of tumour biopsies (Georgakis et al 2006). In DLBCL, phosphorylation of AKT is common (52% to 72% of patient samples) and might be associated with inferior survival (Uddin et al 2006). Mantle cell lymphoma demonstrates variable levels of AKT phosphorylation, although the aggressive blastoid subtype appears to require constitutive AKT activation for survival (Rudelius et al 2006). Follicular lymphoma shows AKT signalling pathway activation, due to either AKT phosphorylation or PTEN downregulation, in the absence of PIK3CA mutations (Yahiaoui et al 2014).

Several studies have demonstrated that a decrease in AKT activity by AKT inhibitors is associated with a reduction in tumour cell proliferation. AKT inhibitors entering clinical development include ipatasertib (RG7440), afuresertib (GSK2110183), uprosertib (GSK2141795), which, like capivasertib, bind to the adenosine triphosphate active site and inhibit AKT activity, thus exerting cytotoxic and antiproliferative activities against human cancer cells. Allosteric inhibitors of AKT have also been studied. Perifosine, MK-2206 and others alter AKT activity through the suppression of cell growth mediated by the inhibition of AKT membrane localisation and subsequent activation (Brown and Banerji 2017). However, limited clinical data are available with AKT inhibitors in lymphoma.

Perifosine is a first-generation AKT inhibitor that functions via inhibition of AKT translocation to the cell membrane (Kondapaka et al 2003). Combined in a phase II trial with the multikinase inhibitor sorafenib, perifosine had an ORR of 28% in relapsed Hodgkin lymphoma (Guidetti et al 2014).

A second-generation AKT inhibitor, MK-2206 functions via allosteric AKT inhibition against AKT1 and AKT2 and has shown strong preclinical activity in a variety of lymphoma cell lines as single agent and in combinations with other agents (Hirai et al 2010; Li et al 2012). MK-2206 monotherapy was tested in a Phase II trial in relapsed or refractory lymphoma

patients (including cHL, MCL, FL and MZL). The study showed that MK-2206 can induce responses in cHL and indolent lymphoma showing a signal of activity with an ORR of 20% in cHL, 22% in indolent lymphoma (one CR in small lymphocytic lymphoma lasting for 3.5 months, and one PR in FL lasting for 5.8 months) and of 9% in MCL. Treatment was overall tolerated; dose-dependent rash, hyperglycaemia and haematological toxicities were most commonly observed (Oki et al 2015).

2.3 Benefit/Risk Assessment

More detailed information about the expected benefits and potential risks of capivasertib may be found in the current capivasertib IB.

2.3.1 Risk Assessment

The risks associated with capivasertib are summarised in Table 1.

Table 1 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study treatment(s) [Capivasertib]		
Risks identified for capivasertib: **Important Identified Risks:** diarrhoea, rash, hyperglycaemia, hypersensitivity. **Identified Risks:** nausea and vomiting, stomatitis, dry skin, pruritus, decreased appetite, erythema multiforme. **Important Potential Risk:** QT prolongation, reproductive organs safety, reproductive and developmental toxicity, genotoxic effects, drug-drug interaction, haematological effects, renal effects or renal failure.	Risks identified based on non-clinical and clinical data available to date and evaluated by AstraZeneca.	These risks are monitored via routine pharmacovigilance and managed via routine risk minimisation activities and standard treatment practices. Further details of these risks can be found in the capivasertib Investigator's Brochure. Risk minimisation activities are reflected in the study protocol specific inclusion and exclusion criteria, alongside the safety monitoring strategy (Section 8), dose modification guidance (Section 6.6), toxicity management guidelines (Appendix G) and concomitant medication guidance (Appendix F).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study treatment(s) [Capivasertib]		
Based on non-clinical data, haematological effects are an important potential risk of capivasertib monotherapy. No association between capivasertib dose and haematological effects have been observed in the ongoing clinical studies to date, involving 887 patients in advanced solid tumour indications (as of 04 Oct 2020).	Within the capivasertib non-clinical programme, effects on the haematopoietic system were noted in rats, with a related decrease in white cells in males. The changes were primarily noted at 100 mg/kg/day dose in males. In the 6 month study decreased cellularity was noted in the thymus and bone marrow of males at 100 mg/kg/day and females 150 mg/kg/day. Changes were reversible with the exception of bone marrow effects. In the dog only the thymus was affected and was fully reversible.	Due to the target population of CAPITAL, and their potential predisposition to cytopenia, either through disease manifestation, or prior anti-cancer treatments, haematological parameters will be closely monitored at regular intervals as specified in the schedule of assessments in the protocol. Haematological toxicity-specific toxicity management guidelines will be included in the protocol to support the Investigator in the clinical management of any such adverse drug reactions secondary to capivasertib. Additionally, enrolled patients will have been screened for adequate bone marrow function prior to commencing capivasertib as per the exclusion criteria in the protocol.

The emerging clinical safety profile from the early clinical studies have not identified risks that would preclude investigation in this setting. Second, the protocol includes ongoing safety monitoring in excess of standard of care monitoring, with the intent of protecting patients involved in the study. Furthermore, dose modification strategy for management of capivasertib-related toxicity and monitoring is in place for those risks deemed to be most likely or serious. Thus, based upon the clinical and non-clinical safety profile, and the strength of the scientific hypothesis under evaluation, the benefit/risk assessment for this study supports the administration of capivasertib in patients with R/R B-cell NHL.

2.3.2 Benefit Assessment

Data from approved PI3K inhibitors support the hypothesis that inhibiting the PI3K-AKT pathway may be a valid target for the treatment of B-cell NHL lymphomas. All 3 PI3K inhibitors approved for R/R FL so far, and the others in development for indolent lymphoma have demonstrated manageable safety and favourable efficacy profiles. Capivasertib targets the same pathway with a potent and over-arching mechanism (all 3 AKT forms). It has

demonstrated a manageable toxicity profile in solid tumours (refer to the current capivasertib IB for details). Also, capivasertib is administered through oral route with an intermittent schedule which may lead to improved patient compliance and ease of patient management in the post-COVID-19 healthcare setting.

Capivasertib has demonstrated clinical activity in several settings, particularly those with tumours harbouring either an AKT1 mutation or PIK3CA mutation (Banerji et al 2018; Hyman et al 2017). In combination, proof of concept was established with first-line paclitaxel in patients with metastatic triple negative breast cancer (Schmid et al 2020) and patients with advanced AKT1 mutant solid tumours in monotherapy or combination with fulvestrant (ER+ breast cancer) (Hyman et al 2017; Smyth et al 2017).

These potential benefits warrant investigation with capivasertib as current data suggests capivasertib is an attractive investigational drug in R/R NHL settings and there is a clear unmet clinical need in this population failing or not being eligible or not having available approved treatment options.

2.3.3 Overall Benefit/Risk Conclusion

While several treatments have been approved for patients with R/R B-cell NHL, none of them currently offer a cure to these patients. Therefore, although monotherapy capivasertib has not been tested so far in lymphoma patients, based on the pre-clinical data available, capivasertib in the R/R B-cell NHL setting does allow the opportunity to assess its activity as monotherapy while offering the patient a reasonable chance of achieving an objective response to the treatment.

Taking into account the measures taken to minimise risk to patients participating in this study, the potential risks identified in association with capivasertib are justified by the anticipated benefits that may be afforded to patients with R/R B-cell NHL. Capivasertib has not been studied yet in the setting of NHL; therefore, this clinical trial will provide the first clinical safety and efficacy data for capivasertib in haematological malignancies.

2.3.4 Benefit/Risk Pertaining to CAPITAL Study Conduct During the COVID-19 Pandemic

Cancer patients have an increased risk of exposure to SARS-CoV-2 due to frequent hospital or clinic visits for treatment and monitoring. A retrospective cohort study of 28 COVID-19-infected cancer patients from 3 hospitals in Wuhan, China, reported that a third of patients (28.6%; N = 8) were suspected to have acquired the infection by hospital-associated transmission (Yu et al 2020, Zhang et al 2020). Patients with cancer may have a higher risk from COVID-19 than individuals without cancer but current evidence appears insufficient to support a conclusive association between cancer in general and COVID-19 (Kumar et al 2019, Xia et al 2020).

CAPITAL will enrol patients with R/R B-cell NHL. Patients in this study will receive interventions that lead to inhibition of AKT (capivasertib). They will not be receiving chemotherapy, radical radiotherapy, immunotherapy or other continuing antibody treatments for cancer as part of the treatment strategy. Overall, the interventions received and procedures during the course of this study are considered to have low risk for increasing susceptibility to COVID-19 infection.

Furthermore, at this stage of disease, patients would typically have frequent healthcare-related visits, irrespective of the participation in a clinical study. Therefore, we anticipate that overall their participation in this clinical study should not significantly increase their risk of exposure to COVID-19 infection. In addition, the dosing regimen for capivasertib involves oral dosing at home (4 days on/3 days off).

Novel treatment options are needed to improve the long-term prognosis for patients with R/R B-cell NHL as this disease stage is associated with high risk of developing debilitating symptoms and cancer-related death. Capivasertib could be a potentially curative treatment option in a R/R patient population with high unmet medical need. The scheduled safety monitoring visits that are considered in excess of standard of care monitoring are intended to protect patients involved in the study. Thus, although there may be increased risk to patients by exposure to SARS-CoV-2 during study visits, this is offset by the benefit that patients may receive in the form of an extended period of PFS.

In accordance with EMA and FDA guidelines (EMA-CTFG-EC 2020, FDA 2020), a risk assessment will be conducted in collaboration with investigators for each site and patient prior to site initiation/patient enrolment and on an ongoing basis throughout the study to assess whether additional measures may be necessary to ensure patient safety and data validity. Measures may include postponement of study start on a global, country, or site level or suspension of recruitment of patients in locations with an increased risk of COVID-19-related disruption.

If there is a need to reconsent study patients for the implementation of new urgent changes in study conduct, additional guidance on alternative means of obtaining reconsent to avoid unnecessary study visits is provided as Appendix A (as a supplement to the standard consent procedures in Appendix A 3 of the protocol). Any deviations to the protocol necessary to safeguard patient safety or data validity as a result of COVID-19-related disruption will be recorded and any permanent changes requiring an amendment to the protocol will be communicated to Regulatory Authorities and IRBs/ECs in line with relevant local guidance and procedures.

3 OBJECTIVES AND ENDPOINTS - CORE

The objectives and estimand descriptions that are common for all study Modules are listed below (Table 2). Refer to individual Modules for the objectives and endpoints specific for each Module.

Table 2 Objectives and Endpoints

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 will include 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, will be included in the assessment of ORR, regardless of whether the patient withdraws from therapy. Patients who go off treatment without a response or progression, receive a subsequent therapy, and then respond will not be 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 will include all patients included in the response evaluable analysis set who had a response, regardless of whether the patient withdraws from therapy. The measure of interest is the median DoR.

Objectives	Estimand description
	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.
• 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 will include all dosed patients, regardless of whether the patient withdraws from therapy, receives another anti-lymphoma therapy or clinically progresses 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 will include all dosed patients, regardless of whether the patient withdraws from therapy or receives 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	Patient-reported disease-related symptoms, functioning and health-related quality of life as measured by EORTC QLQ-C30. The analysis will include all dosed patients and will 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 time point.
• To assess patient-reported symptomatic AEs/tolerability of module-defined study treatment in each cohort	Patient-reported symptomatic AEs and overall side effect burden as measured by PGI-TT and selected items from PRO-CTCAE. The analysis will include all dosed patients and will be summarised descriptively.

Objectives	Estimand description
	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 time point.
• To estimate the effectiveness of the module-defined study treatment by assessment of TFST in each cohort	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 will include all dosed patients regardless of whether the patient withdraws from therapy, receives another anti-lymphoma therapy or clinically progresses 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	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 will include all patients included in the response evaluable analysis set who had a response regardless of whether the patient withdraws 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 will include all dosed patients and will be summarised descriptively.
Pharmacokinetic	
• 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).

Objectives	Estimand description
	Plasma PK parameters derived from a population PK model, as permitted by the data.
Exploratory	
• CCI	CCI
• CCI	CCI
• CCI	CCI
• CCI	CCI CCI CCI
• CCI	CCI CCI CCI
• CCI	CCI CCI CCI
• CCI	CCI

[a] Cheson et al 2014.

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

4 STUDY DESIGN - CORE

4.1 Overall Design

4.1.1 Master Protocol Structure

This study is an open-label, multicentre Phase II study of capivasertib administered orally in patients with R/R B-cell NHL. The structure of the protocol follows a modular design. Patients will be enrolled concurrently in the individual cohorts according to the type of NHL.

For an overview of the study design, see Figure 1, Section 1.2.

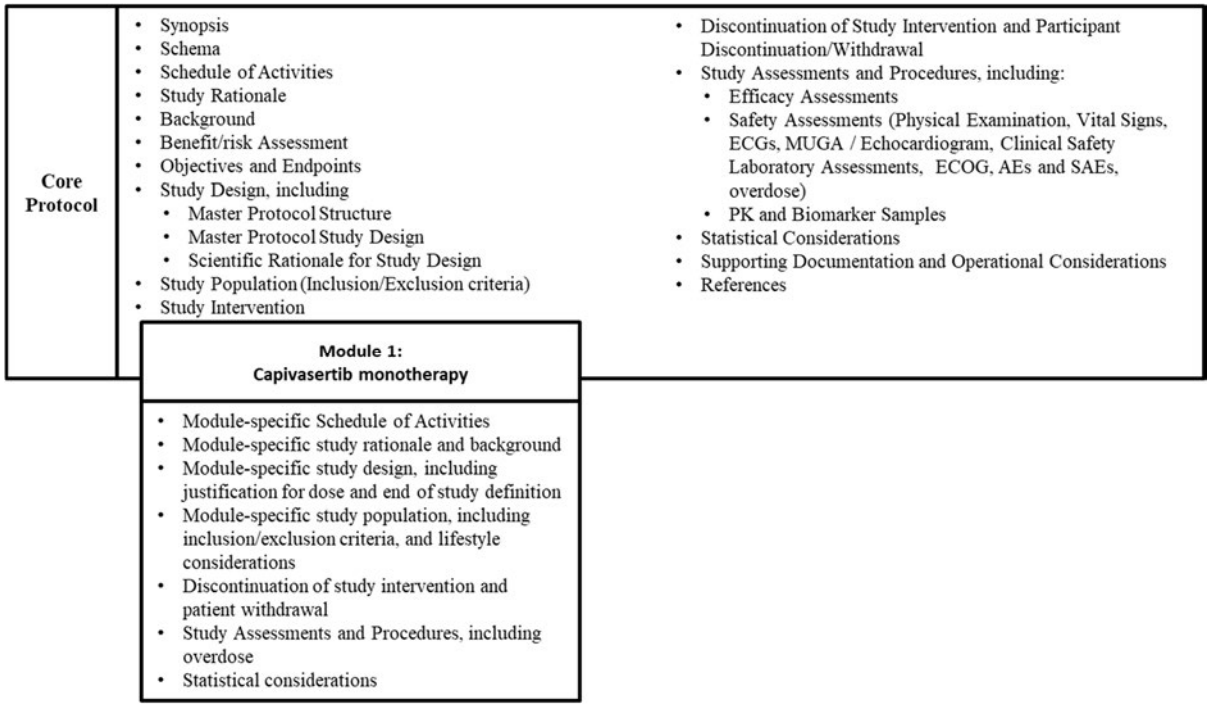
4.1.2 Master Protocol Study Design

This protocol, hereafter referred to as the "Core Protocol" describes core study elements that are applicable to all study treatments that will be provided under the study. In addition to the Core Protocol, individual complementary "Modules" contain elements specific to each individual cohort (Figure 2).

The information in this Core Protocol cannot be superseded by information in the Modules. Any change to the study core elements (ie, this Core Protocol) or Modules will be submitted to regulatory authorities and ethics committees according to the local legislation/requirements.

Other Modules assessing capivasertib in combination with other agents in patients with R/R B-cell NHL may be further added via formal protocol amendments based on emerging supportive preclinical and clinical data and study rationale.

Figure 2 Protocol Modular Structure



AE: adverse event; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; MUGA: multiple-gated acquisition; PK: pharmacokinetic(s); SAE: serious adverse event.

4.1.3 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the patient's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study patients, maintain compliance with GCP, and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the ICF should be signed at the patient's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened patients. The investigator should confirm this with the designated Study Physician.
- Home or Remote visit: Performed by a site qualified HCP or HCP provided by a TPV.
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home study treatment administration: Performed by a site qualified HCP, HCP provided by a TPV, or by the patients or the patient's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix H.

4.2 Scientific Rationale for Study Design

The study will consist of modules, each evaluating the efficacy, safety and tolerability of study treatment given to patients with different types of lymphoma.

The study will include module-specific interim analyses. These interim analyses will be assessed against a decision framework (Frewer et al 2016). Based on the interim results, study enrolment could pause and the sponsor may opt to amend the protocol to adjust dosing schedule based on emerging data, permanently close one or more cohorts or add in a new cohort evaluating capivasertib in another type of lymphoma or a new module evaluating capivasertib in combination with other agents in that population. These new cohorts and/or modules may be further added via formal protocol amendments based on emerging supportive preclinical and clinical data and study rationale.

4.2.1 Regulatory Amendments for Additional Modules

To support amendments of the protocol for additional Modules, AstraZeneca will provide a summary of non-clinical and clinical data to support the proposed new combination and dosing schedule; this will include updating the following:

- Study objectives
- Background information providing rationale for the proposed patient population(s) and the proposed treatment plan(s)
- Specific study eligibility criteria
- A detailed description of the proposed study treatment plans

- A revised schedule of patient assessments
- A summary of safety data from the completed or ongoing cohort(s)/Modules(s) and the proposed toxicity management plans for the proposed new combination
- A description of any dose modifications and the data (clinical safety information, clinical PK data, and non-clinical data) that support the safety of the proposed dose modifications for the combination/monotherapy regimen in question
- A clearly stated justification for the proposed sample size based on the objectives for that specific cohort/module; and
- A detailed description of the method and performance characteristics of any test that will be used to identify the patient population to be enrolled in the cohort/Module, if the population will be selected based on a diagnostic assay.

4.2.2 Europe and rest of the World

AstraZeneca will provide a substantial amendment for review and approval.

4.2.3 United States of America

AstraZeneca will provide an amendment to the FDA 30 days in advance of planned enrolment in the cohort for any future combination. AstraZeneca will begin enrolment of patients into that cohort in the US no sooner than 30 days from the date of submission and IRB approval.

4.3 Justification for Dose

Refer to the relevant Module in the protocol for information.

4.4 End of Study Definition

The end of study is defined as the last visit of the last patient in the study or last scheduled procedure shown in the SoA in the relevant Module for the last patient in the study globally.

A patient is considered to have completed the study when the patient has completed his/her last scheduled procedure shown in the SoA in the relevant Module, including follow-up for OS.

The study may be stopped if, in the judgement of AstraZeneca, study patients are placed at undue risk because of clinically significant findings.

Refer to the relevant Module for further information.

5 STUDY POPULATION - CORE

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

The inclusion and exclusion criteria specific to each cohort are provided in the relevant Module.

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for both the Core Protocol and relevant Module. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4.

5.1 Core Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

Age

1 Patient must be ≥ 18 years of age, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 ECOG performance status ≤ 2.

3 Life expectancy > 6 months.

Sex

4 Male and female.

Reproduction

5 Female patients of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study interventions) and intend to be sexually active with a non-sterilised male partner are required to use 1 form of highly effective method of contraception combined with a barrier method (male condom, female condom, cervical cap, diaphragm with spermicide, or contraceptive sponge with spermicide) of contraception from the time of screening until 4 weeks after the last dose of study treatment (see Section 5.3.4).

OR

Female patient must be classified as non-childbearing potential by fulfilling 1 of the following criteria at screening:

- Post-menopausal – defined as aged > 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.
- Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy, but not tubal ligation.

6 Female patients must not be breast-feeding and must have a negative pregnancy test (serum) prior to start of dosing.

7 Non-sterile male patients should use barrier contraception (ie, condoms) from the time of screening until 16 weeks after last dose of study treatment. Male patients must not donate or bank sperm during this same time period. It is not known whether the preclinical changes seen in the male animal reproductive organs, after treatment with capivasertib, will be fully reversible or will permanently affect the ability to produce healthy sperm following treatment. Therefore, if male patients may wish to father children in the future, they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

Informed Consent

8 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

9 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research.

- If a patient declines to participate in this optional exploratory research and genetic component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

Optional Genetic Research

10 Whole blood transfusion given within 120 days of genetic sample collection should be leukocyte depleted.

5.2 Core Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Prior malignancy (other than the disease under study), except for adequately treated basal cell or squamous cell skin cancer, in situ cancer, or other cancer from which the patient has been disease free for ≥ 2 years.

2 Major surgical procedure or significant traumatic injury (as judged by the investigator) within 28 days before start of treatment, or have not recovered from major side effects, open biopsy within 7 days before start of treatment.

3 With the exception of alopecia, any unresolved non-haematological toxicities from prior therapy ≥ CTCAE Grade 2 at the time of starting study treatment.

4 Known medically apparent CNS lymphoma or leptomeningeal disease.

5 Any of the following cardiac criteria at screening:

a) Mean resting QTc > 470 ms obtained from 3 consecutive ECGs.

b) Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (eg, complete left bundle branch block, third degree heart block).

c) Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia of Grade ≥ 1, potential for Torsades de Pointes, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age, history of QT prolongation associated with other medications thar required discontinuation of that medication, or any concomitant medication known to prolong the QT interval.

d) Experience of any of the following procedures or conditions in the preceding 6 months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure NYHA grade ≥ 2.

e) Uncontrolled hypotension – SBP < 90 mmHg and/or DBP < 50 mmHg.

f) Cardiac ejection fraction outside institutional range of normal or < 50% (whichever is higher) as measured by ECHO (or MUGA scan if an ECHO cannot be performed or is inconclusive).

g) History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Participants with atrial fibrillation controlled by medication or arrhythmias controlled by pacemakers may be permitted upon discussion with the study physician.

6 Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values at screening:

a) ANC < 1.0×10^9/L; < 0.75×10^9/L in patients with known bone marrow involvement of malignant disease.

Note: The use of growth factors is permitted at the Investigator's discretion.

b) Platelets < 75×10^9/L; < 50×10^9/L in patients with known bone marrow involvement of malignant disease

c) Anaemia that cannot be managed by standard supportive care.

d) ALT or AST > 2.5 × ULN; > 5 × ULN for patients with liver involvement of metastatic disease.

e) Total bilirubin > 1.5 × ULN or > 3 × ULN for patients with liver involvement of metastatic disease or in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia).

f) Creatinine clearance < 50 mL/min per the Cockcroft and Gault formula.

7 Clinically significant abnormalities of glucose metabolism as defined by any of the following at screening:
   a) Patients with diabetes mellitus type I or diabetes mellitus type II requiring insulin treatment
   b) HbA1c ≥ 8.0% (63.9 mmol/mol)

8 As judged by the investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, or active infection including SARS-CoV-2, CMV, hepatitis B, hepatitis C. Patients with HIV infections are excluded.

   Note:
   - Patients who are anti-HBc antibody positive and who are surface antigen negative will need to have a negative PCR result before enrolment.
   - Those who are hepatitis B surface antigen positive or hepatitis B PCR positive will be excluded.
   - Patients who are hepatitis C antibody positive will need to have a negative PCR result before enrolment. Those who are hepatitis C PCR positive will be excluded.

9 Refractory nausea and vomiting, malabsorption syndrome, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection, or other condition that would preclude adequate absorption of capivasertib.

10 Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, may affect the interpretation of the results, render the patient at high risk from treatment complications or interferes with obtaining informed consent.

11 Evidence of dementia, altered mental status or any psychiatric condition that would prohibit understanding or rendering of informed consent.

Prior/Concomitant Therapy

12 Prior treatment with any of the following:
   a) Any investigational agents or study drugs from a previous clinical study within 5 half-lives or 2 weeks from the first dose of capivasertib in this study.
   b) Any other chemotherapy, immunotherapy, immunosuppressant medication (other than corticosteroids) or anti-cancer agents within 2 weeks of the first dose of study treatment. A longer washout may be required for drugs with a long half-life (eg, biologics) as agreed by the sponsor. Any treatment-related toxicity from a prior therapy with PI3K inhibitor should be resolved at the time of study entry. Patients previously treated with BTK inhibitors can start the study treatment immediately.

Earlier initiation of study treatment will be discussed case by case with the Study Physician.

c) Strong inhibitors or inducers of CYP3A4 within 2 weeks prior to the first dose of study treatment (3 weeks for St John's wort), or drugs that are sensitive to inhibition of CYP3A4 within 1 week prior to the first dose of study treatment. For details, see Appendix F.

d) Prior allogenic HSCT within 6 months from the first dose of capivasertib (patients > 6 months after allogenic HSCT are eligible in the absence of active graft-versus-host disease and concomitant immune-suppressive therapy). Prior cellular therapies (eg, CAR-T therapy) and/or autologous HSCT within 3 months from the first dose of capivasertib.

e) Receipt of live, attenuated vaccine within 28 days before the first dose of study treatment(s).

f) Patients who, due to other medical conditions /prior history /concomitant medications are, in the investigator's opinion, at a risk of a VTE and are not willing to accept the VTE prophylaxis, will be excluded.

Note: The initiation of an adequate VTE prophylaxis will be based on treating physician risk/benefit assessment and in agreement with the local management guidelines.

Prior/Concurrent Clinical Study Experience

13 Participation in another clinical study with an IMP administered in the last 2 weeks or 5 half-lives, whichever is longer.

14 History of hypersensitivity to active or inactive excipients of capivasertib or drugs with a similar chemical structure or class to module-defined study treatment(s).

Diagnostic Assessments

Not applicable.

Other Exclusions

15 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

16 Judgement by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements.

17 Previous enrolment in the present study.

18 For women only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

5.3 Lifestyle Considerations

The following restrictions apply while the patient is receiving capivasertib and for the specified times before and after:

5.3.1 Meals and Dietary Restrictions

There is a potential for delayed and reduced absorption and/or amplified effects on the glucose homeostasis if capivasertib is administered with food, in particular together with heavy meals. The clinical relevance of this is unknown, but until further information is available a conservative approach has been taken to recommend that patients fast from 2 hours before dosing to 1 hour after dosing, where possible.

In addition, patients should avoid herbal supplements (eg, St John's wort) and ingestion of large amounts of foods and beverages known to potently modulate CYP3A4 and/or UGT2B7 enzyme activity during study treatment. For example, no more than half a grapefruit, a small glass of grapefruit juice, or 2 teaspoons of Seville orange marmalade should be consumed daily.

5.3.2 Caffeine, Alcohol, and Tobacco

No interactions with caffeine, alcohol, or tobacco have been identified.

5.3.3 Activity

Not applicable.

5.3.4 Pregnancy and Contraception

5.3.4.1 Females

Women of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study interventions) and intend to be sexually active with a non-sterilised male partner are required to use one form of highly effective contraception combined with a barrier method (male condom, female condom, cervical cap, diaphragm with spermicide, or contraceptive sponge with spermicide) of contraception starting before entering the study and until 4 weeks after the last dose of capivasertib. Table 3 contains appropriate contraception options when participating in this study.

It is not known whether capivasertib has the capacity to affect the metabolism of hormonal contraceptives, so the highly effective contraception method selected from Table 3 must also be combined with a barrier method of contraception.

Table 3 Acceptable Highly Effective Contraception Options

Acceptable non-hormonal birth control methods:
• Total/true abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the study treatment and for at least 4 weeks (for female patients) or at least 16 weeks (for male patients) after the last dose of study treatment. Periodic abstinence (eg, calendar ovulation, symptothermal, post ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception. • Vasectomised sexual partner (with patient assurance that partner received post-vasectomy confirmation of azoospermia) combined with a barrier method. • Bilateral tubal occlusion combined with a barrier method. • Intrauterine device (provided coils are copper banded) combined with a barrier method.
Acceptable hormonal methods:
• Mini pill combined with a barrier method: Progesterone-based oral contraceptive pill using desogestrel. Cerazette (Merck Sharp & Dohme) is currently the only highly efficacious progesterone-based pill available. • Combined pill combined with a barrier method: Normal and low-dose combined oral pills. • Injection combined with a barrier method: Medroxyprogesterone injection. • Patch combined with a barrier method: Norelgestromin/ethinyl estradiol transdermal system. • Implants combined with a barrier method: Etonorgestrel-releasing implants. • Intravaginal device (eg, ethinyl estradiol-/etonogestrel-releasing intravaginal devices) combined with a barrier method. • Levonorgestrel-releasing intrauterine system combined with a barrier method.

5.3.4.2 Males

Non-sterile men who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study interventions) and intend to be sexually active with a female partner (of childbearing potential) must use a condom upon entering the study and until 16 weeks after the last dose of capivasertib. Contraception should be used in females' partners of men taking capivasertib who are of childbearing potential during the course of the study and for 16 weeks after the final dose of capivasertib (see Table 3 for recommended contraception options for female partners).

Even if the female partner is pregnant, male patients should still use a condom plus spermicide (if available in your country), as indicated above during the clinical study.

Male patients should refrain from donating sperm from the start of dosing until 16 weeks after last dose of study treatment.

5.3.5 Other Restrictions

Patients who are blood donors should not donate blood during the study and for 3 months following their last dose of study treatment.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Patients may be rescreened a single time. However, rescreening should be documented so that its effect on study results, if any, can be assessed. These patients should have the reason for study withdrawal recorded as screen failure in the eCRF. Rescreened patients should be assigned the same patient number as for the initial screening.

6 STUDY INTERVENTION - CORE

Study intervention is defined as any investigational intervention, marketed product or placebo intended to be administered to or medical devices utilised by a study patient according to the study protocol.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

All patients will receive treatment with the investigational product capivasertib. Refer to the relevant Module for further details.

Capivasertib Dosing Instructions

Capivasertib tablets should be swallowed whole, not crushed, with a glass of water. Where possible, all doses of capivasertib should be taken at approximately the same time each day, 12 hours apart in a fasted state (water to drink only) from at least 2 hours prior to the dose to at least 1 hour post-dose. Additional fasting restrictions apply on days where fasting glucose is to be tested (Section 8.2.4.1).

If vomiting occurs, a replacement dose should not be taken, and the patient should take their allotted dose at the next scheduled time.

Should a patient miss a scheduled dose, the patient will be allowed to take the dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken, and the patient should take their allotted dose at the next scheduled time. If a patient needs to take the dose earlier for whatever reason, the patient can take the dose up to 2 hours earlier than the scheduled dose time. The patient should make every reasonable effort to take the capivasertib tablets on time.

Permitted capivasertib dose modifications are described in Section 6.6.

6.2 Preparation/Handling/Storage/Accountability

1) The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2) Only patients enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
3) The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4) Further guidance and information for the final disposition of unused study treatments are provided in the relevant Module and the Pharmacy Manual.

6.3 Measures to Minimise Bias: Randomization and Blinding

This is an open-label, non-randomised study; no blinding is required.

6.4 Study Intervention Compliance

When patients are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the study site will be recorded in the source documents and recorded in the eCRF. The dose of study treatment and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

Patients will receive a drug diary to record the specific time each dose was taken and to record reasons for any missed doses. The patient will be instructed to bring the diary and any remaining study treatment to the clinic at their next visit.

When patients self-administer study treatment at home, compliance with study treatment will be assessed at each visit. Compliance will be assessed by counting returned tablets during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of capivasertib tablets dispensed to and taken by each patient must be maintained and reconciled with study treatment and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded

in the eCRF.

The Investigational Product Storage Manager is responsible for managing the study treatment from receipt by the study site until the destruction or return of all unused study treatment.

The investigator is responsible for ensuring that the patient has returned all unused study treatment.

Refer to the relevant Module for details.

6.5 Concomitant Therapy

Any concomitant treatment, procedure, or other medication considered necessary by the investigator for the patient's safety and wellbeing, or vaccine (including over-the-counter or prescription medicines, blood transfusions, vitamins, and/or herbal supplements) that the patient is receiving within 4 weeks prior to the first dose of study treatment or receives during the study including the 30-day follow-up period following the last dose of study treatment must be recorded in the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

If any concomitant therapy is administered due to new or unresolved AE, it should be recorded. Investigational agents (eg, investigational agents to treat the underlying disease) are not permitted until EOT.

Patients must be instructed not to take any medications, including over-the-counter products or herbal remedies, without first consulting with the investigator.

Potential interactions of capivasertib with concomitant medications and restricted, prohibited and permitted concomitant medications are described in Appendix F.

6.5.1 Drugs that Prolong QT Interval

Due to the important potential risk of QT prolongation derived from the capivasertib non-clinical development programme, it is recommended that administration of any drugs (at screening or during study conduct) considered essential for patient management which are known to prolong the QT interval is discussed with the AZ Study Physician and that consideration should be given for close monitoring of QT interval prolongation through

frequent ECG and electrolyte monitoring.

During screening, the drugs that patients are currently using (prescription and non-prescription) should be checked against the ArizonaCert website. In addition, drugs intended for use during study treatment should be checked against the website. (https://www.crediblemeds.org/).

6.6 Dose Modification

Refer to the relevant Module for further details and Appendix G.

6.7 Intervention After the End of the Study

After discontinuation of study treatment (see Section 7.1), the investigator will be at liberty to further define the most appropriate anti-lymphoma treatment. Information on subsequent anti-lymphoma therapies should be recorded in the clinical database. Efficacy assessments should continue until PD, even if patients start another anti-lymphoma therapy.

No intervention is planned after the end of the study. However, provisions will be in place for patients still enrolled at the end of the study to continue to receive study treatment if, in the opinion of the investigator, they are continuing to receive benefit from treatment.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with study treatment may be transitioned to such study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visits and assessments per its protocol. Any patients who would be proposed to move to such study would be asked to sign a new ICF.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL - CORE

7.1 Discontinuation of Study Intervention

Patients must be discontinued from study treatment in the following situations:

- Patient decision: The patient is at any time free to discontinue study treatments, without prejudice to further treatment.
- Pregnancy (see Section 8.3.11.1).
- Any AE that meets criteria for discontinuation defined in those modification guidelines for management of capivasertib-related toxicity (see Appendix G).
- Objective disease progression assessed by investigator per the Lugano 2014 Classification for NHL (Cheson et al 2014).

- Severe noncompliance with the CSP in the judgement of the investigator and/or the sponsor.
- Patients incorrectly initiated on study treatments.
- Intercurrent illness that, in the judgement of the investigator, will affect assessments of clinical status to a significant degree or contraindicate further dosing.
- Unacceptable toxicity.
- Determination by the investigator that it is no longer safe for the patient or in the patient's best interest to continue therapy.
- Clinical need for concomitant or ancillary therapy that is not permitted in the study.
- Initiation of subsequent anti-lymphoma therapy, including another investigational agent.
- Death.
- General or specific changes in the patient's condition that are unacceptable for further treatment in the judgement of the investigator.

Note that discontinuation from study treatment is NOT the same thing as a withdrawal from the study. If study treatment is permanently discontinued, the patient will remain in the study to complete the EOT visit within 7 days of discontinuation of study treatment, the post-treatment follow-up (30 [± 7] days after last dose) and the long-term follow-up every 12 weeks.

See the SoA in the relevant Module for data to be collected at the time of intervention discontinuation (EOT) and long-term follow-up, and for any further evaluations that need to be completed.

Refer to relevant Module for criteria for stopping or pausing the study recruitment.

7.1.1 Temporary Discontinuation

Refer to the relevant Module for details.

7.2 Participant Withdrawal from the Study

- A patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A patient who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an EOT visit should be conducted, as shown in the SoA. See SoA in the relevant Module for data to be collected at the time

of study withdrawal and follow-up and for any further evaluations that need to be completed.

  - The patient will discontinue the study treatment and be withdrawn from the study at that time.

- If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a patient withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

Refer to the relevant Module for details.

7.3 Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the study site for a required study visit:

- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomised, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the patient will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES - CORE

- Study procedures and their timing are summarised in the SoA in the relevant Module. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA in the relevant Module, is essential and required for the study.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA, with the exception of bone marrow aspirates/biopsies (up to 12 weeks before the first planned dose of study treatment).
- Any imaging assessments (eg PET/CT scan) performed prior to the ICF signature within 5 weeks may be considered as baseline, provided that:
  - no anti-lymphoma treatment (including radiotherapy) has been administered between the date of the assessment and the first planned dose (with the only exception of low-dose steroids ie, < 10 mg prednisolone or equivalent).
  - there is no significant clinical worsening of the patient.

Disease-specific assessment at screening include collection of prior lines of anti-cancer therapies, with their best overall response and relapse date and disease prognostic scores (Appendix J).

All efficacy assessments should continue until progression, even if patients stop study treatment.

8.1 Efficacy Assessments

Efficacy assessments will be performed as indicated in the SoA in the relevant Module until disease progression or relapse, death, lost to follow-up or withdrawal of the consent.

Disease status at baseline and during the study will be evaluated by using:

- Physical examination: attention to node-bearing areas, including Waldeyer's ring, and to the size of liver and spleen
- Total body CT, whole body FDG-PET, MRI
- Brain imaging (MRI with contrast will be performed at screening only if there is a prior history of CNS involvement or if there are neurologic signs or symptoms present or as clinically indicated during the study)
- Bone marrow biopsy and/or aspirate (Section 8.1.1)
- Endoscopic and histopathologic assessments (eg, tumour biopsy, cytology) if applicable

8.1.1 Bone Marrow Assessments

For all patients, a baseline (before first dose of study treatment) bone marrow biopsy and/or aspirate is required at screening to assess bone marrow involvement by lymphoma.

Bone marrow biopsies/aspirates will be read at each site's local laboratory and will be performed as clinically indicated while on study (ie, to confirm CR (if bone marrow was involved by lymphoma at baseline, within 28 days after the respective radiological assessment) and per standard of care. Furthermore, if bone marrow involvement before the start of the study was unknown, a bone marrow evaluation must be conducted to confirm a CR.

Patients with a negative bone marrow aspirate/biopsy (ie, no lymphoma involvement) at screening, and patients with a PR, SD or PD at any disease response assessment time point do not require a follow-up bone marrow aspirate/biopsy. Locally obtained results should be entered into the eCRF.

Further details on sample processing, handling and shipment are provided in the Manual.

8.1.2 Imaging Assessments

During the screening period, a PET-CT scan will be performed to assess the measurability of disease and will serve as baseline (Day -28 to Day -1). Information on extranodal involvement will also be recorded.

Subsequent radiological assessment, ie, CT scans with contrast (unless contraindicated) covering neck, chest, abdomen, and pelvis and any other disease sites will be performed every 8 weeks (± 7 days) until Week 24 (ie, Weeks 8, 16, and 24), every 12 weeks (± 7 days) until Week 60 (ie, Weeks 36, 48 and 60) and thereafter every 12 weeks (± 7 days) for R/R MCL and every 24 weeks (± 7 days) for R/R FL/MZL.

Patients who discontinue study intervention for reasons other than PD will continue to be scanned for disease response until documented PD and regardless of starting a new

anti-lymphoma treatment following the same schedule, ie, every 8 weeks (± 7 days) until Week 24 (ie, Weeks 8, 16, and 24), every 12 weeks (± 7 days) until Week 60 (ie, Weeks 36, 48 and 60) and thereafter every 12 weeks (± 7 days) for R/R MCL and every 24 weeks (± 7 days) for R/R FL/MZL.

PET scans covering whole body from base of skull to mid-thigh (or PET/CT scans) are mandatory every 8 weeks (± 7 days) until Week 24 (ie, Weeks 8, 16, and 24) and thereafter to confirm CR or as clinically indicated. More frequent PET-CT scan can be performed when clinically indicated at the investigator's discretion.

For MZL patients with FDG-avid disease at baseline, disease response to study treatment will be based on both PET and CT-based criteria. For MZL patients with no FDG-avid disease at baseline, disease response to study treatment will be based on CT-based criteria only.

PET scans should be performed whenever possible at during the 3 days off of study treatment. If a PET/CT is not available, an independent PET and a diagnostic-quality CT scan can be used. If PET and CT scans are done on the same day, the PET is recommended to be performed prior to the contrast-enhanced CT not to compromise the PET read-out. If the time between a contrast enhanced CT and a PET is long enough (eg, > 6 hours), it is possible to perform CT with IV contrast prior to the PET scan.

The CT portion of a PET/CT may be submitted in lieu of a dedicated CT; however, certain radiographic requirements are needed for acceptance, as described in the Site Radiology Manual, provided separately from this protocol.

MRI may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations).

No anti-cancer treatment other than study treatment can be implemented between the earliest date of baseline scans or bone marrow assessment and the start of study treatment. Patients should have radiographic tumour measurements done at the participating study centre or an acceptable alternate imaging facility using an identical imaging protocol and similar equipment. The same imaging equipment should be used for all scans whenever possible. The same radiologist should be assigned to read all the scans for a given patient throughout the study.

All images for the assessment of response will be collected and stored for BICR. Any unscheduled efficacy assessment will also be sent for BICR to an AstraZeneca-designated imaging CRO. De-identified copies of all radiology results may be requested by the sponsor.

8.1.3 Disease Response Assessment

8.1.3.1 Lugano 2014 Classification for Non-Hodgkin Lymphomas

The assessment of response per the Lugano 2014 Classification for NHL (Cheson et al 2014 and Appendix I) will be used to determine the anti-tumour activity of study treatment.

The efficacy endpoints are based on the overall response assessment (Appendix I).

8.1.4 Other Disease-specific Assessments

8.1.4.1 Endoscopy

Endoscopy with adequate tissue sampling for histopathologic analysis is mandatory to confirm CR for any patients with a documented history of gastrointestinal involvement. After CR is confirmed histologically (biopsy to be performed within 28 days from the respective radiological assessment), subsequent endoscopic assessments are not mandatory for disease evaluation, unless there is suspicion of a new or recurrent gastrointestinal involvement.

8.1.4.2 CCI

CCI

CCI

CCI

8.1.4.3 B-symptoms

B-symptoms are constitutional symptoms defined as any one or more of the following disease-related symptoms or signs:

- Unintentional weight loss of 10% or more within the previous 6 months
- Significant fatigue (ie, ECOG performance status 2 or worse; inability to work or perform usual activities)
- Fevers > 100.5°F or 38.0°C for ≥ 2 weeks without other evidence of infection
- Night sweats for > 1 month without evidence of infection

B-symptoms should not be reported as AEs and will be collected at each disease response assessment during treatment and as clinically indicated.

8.1.5 Clinical Outcome Assessments

A COA is any assessment that may be influenced by human choices, judgement, or motivation

and may support either direct or indirect evidence of treatment benefit. Clinical outcome assessments can be reported by a patient (PRO), a clinician (Clinician-reported Outcome), an observer (Observer-reported Outcome), or through a performance based assessment (FDA-NIH BEST Resource). A COA may be used in clinical studies to provide either direct or indirect evidence of treatment benefit. It is important to examine the impact of therapy on symptoms, function, and other health-related QoL of the patient to aid understanding of the risk benefit profile.

Patient-reported outcome is one type of COA and is a general term referring to all outcomes and symptoms that are directly reported by the patient. Patient-reported outcome s have become important in evaluating the effectiveness of study treatment in clinical studies and will aid in understanding of the benefit/risk evaluation (Kluetz et al 2018). The following PRO instruments will be administered in this study:

- Health-related QoL questionnaire EORTC QLQ-C30
- CCI
- NCI PRO-CTCAE
- Patient-reported anti-diarrhoeal medication
- PGI-TT
- CCI
- CCI
- CCI

Patient-reported outcomes will be administered according to the SoA. The PRO questionnaires will be completed by patients if a linguistically-validated version is available in their language for the country in which they live. The individual questionnaires are provided in Appendix K.

8.1.5.1 EORTC QLQ-C30

The EORTC QLQ-C30 was developed by the EORTC QoL Group 1993. It consists of 30 items and measures symptoms, functioning, and global health status/QoL (Aaronson et al 1993) for all cancer types. Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social), 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting), a 2-item global QoL scale, 5 single items assessing additional symptoms commonly reported by cancer patient (dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea), and 1 item on the financial impact of the disease. The EORTC QLQ-C30 is a valid and reliable PRO instrument in this patient population.

8.1.5.2 CCI

CCI

CCI [redacted]

8.1.5.3 PRO-CTCAE

The PRO-CTCAE system has been developed by the NCI and is included to assess tolerability from the patients' perspective. The PRO-CTCAE will only be administered in those countries where a linguistically validated version is available. PRO-CTCAE is an item library of symptoms experienced by patients while undergoing treatment of their cancer. It has been carefully and systematically developed based on the NCI CTCAE to provide patient reported assessment of common adverse effects of cancer treatments, including a library of 124 items, representing 78 symptomatic toxicities. The items have previously undergone extensive qualitative and quantitative evaluation to support their validity and reliability (Basch et al 2014; Dueck et al 2015; Hay et al 2014). For each symptomatic AE (eg, headache), there are up to three questions related to key symptom attributes, including the symptom frequency, severity, and interference with daily activates. Each question uses a 7-day recall with a 5-point ordinal response scale. The items pre-selected for this study are based on a review of the core symptom set from NCI, expected treatment related symptoms, and in consideration of symptoms that are already captured in the other PRO instruments with a view to minimize patient burden. Pre-selected items that will be administered in this study include dry mouth, blurred vision, headache, urinary frequency, diarrhoea, decreased appetite, nausea, vomiting, fatigue, dry skin, rash and itching. The free text item in the PRO-CTCAE instrument is not included in the study, as the utility of this information and the analysis method have not been established.

The PRO-CTCAE is intended to enhance the precision and reproducibility of adverse event reporting to provide data that complements and extends the information provided by clinician-reporting using CTCAE, and to represent the patient perspective of the experience of symptomatic adverse events. Signs and symptoms assessed with the PRO questionnaires will not be considered AEs unless entered as such into the eCRF. Use of PRO-CTCAE is limited to describing in aggregate the safety and tolerability of the study drugs and does not include the use of PRO-CTCAE for diagnostic, prognostic, or therapeutic purposes in human subjects, or the use of PRO-CTCAE to assess the efficacy of the study drugs.

8.1.5.4 Patient-reported anti-diarrhoeal medication

A question is included to capture patient-reported anti-diarrhoeal medication over the past 1 week: "Did you take any medicine for diarrhoea?". Patients will be asked to choose the responses of "Yes" or "No". If yes, patients will be asked "how much did it help?" with response options: not at all, a little, quite a bit, very much. The questions are included to aid in the interpretation of patient-reported diarrhoea.

8.1.5.5 PGI-TT

The PGI-TT item is included to assess how a patient perceives the overall burden of treatment-related side effects of cancer treatment over the past 1 week. Patients will be asked to choose the response that best describes the level of burden by the side effect of their cancer treatment over the past week. The response options are: not at all, a little bit, somewhat, quite a bit, and very much. This item is included to aid in the interpretation of other PRO measures and to evaluate the overall impact of treatment-related side effects.

8.1.5.6 CCI

CCI

8.1.5.7 CCI

CCI

8.1.5.8 CCI

CCI

CCI

8.1.5.9 Administration of Electronic PRO Questionnaires

Electronic PROs will be self-administered at home by the patients using handheld devices at the time points indicated in the SoA in the relevant Module. Patients may complete the ePROs at study sites if the assessment time point coincides with a scheduled site visit; otherwise, patients should complete the ePROs at home. Similarly, during the follow-up period, patients should complete ePROs at home or at the study site if a scheduled visit coincides with the time point.

Patients must be instructed to bring the device to all visits.

The instructions below should be followed when collecting PRO data via an electronic device:

- PRO questionnaires must be completed prior to any other study procedures or discussions (following informed consent), including medication treatments, and before discussion of PD to avoid biasing the patient's responses to the questions.
- PRO questionnaires should be completed by the patient in a quiet and private location.
- The patient should be given sufficient time to complete the PRO questionnaires at his/her own speed.
- The research nurse or appointed site staff should explain to patients the value and relevance of these data so that they are motivated to comply with questionnaire completion.
- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if the participant has any medical problems, he/she should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the patient on how to use the ePRO device using the materials and training provided by the ePRO vendor.
- The research nurse or appointed site staff must provide guidance on whom to call if there are problems with the device when the patient is completing the ePRO at home.
- All PRO questionnaires are to be completed electronically. If technical or other device-related issues prohibit completion on the device, appropriate back-up options may be considered with prior approval from AstraZeneca.
- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and avoid introducing bias by not clarifying items.
- The patient must not receive help from relatives, friends, or study site staff to answer the ePRO questionnaires. If a patient uses visual aids (eg, spectacles or contact lenses) for reading and does not have them when he or she attends the study site, the patient will be exempted from completing the ePROs at that study site visit.
- Site staff must not read or complete the ePRO questionnaires on behalf of the patient. If the patient is unable to read the questionnaire (eg, is blind, illiterate or not fluent in the available language), that patient is exempted from completing PRO questionnaires but may still participate in the study. If the patient cannot complete the PRO questionnaires due to reasons other than being blind, illiterate, or fluent in language, the AstraZeneca study team must be contacted to determine if they can be exempted. Patients exempted in this regard should be flagged appropriately by the site staff in the source documents and in the designated eCRF.

- Site staff must administer questionnaires available in the language that the patient speaks and understands. Questions must not be read in an available language and translated into another language for the patient.
- It is vital that the ePRO reporting is initiated at the baseline visit, as specified in the SoA in the relevant Module to capture the effect of study treatment.
- Reminders should be sent to patients at home as needed to ensure compliance with the assessment schedules.

Finally, the research nurse or appointed site staff will review the completion status of questionnaires during site visits, and document the reason(s) why a patient could not complete assessments, in the source documents and in the designated eCRF. If the site receives an email notification regarding the patient's compliance, appropriate action should be taken (eg, discussion with patient to improve compliance, a check-in call from the site to ask the patient if they have any difficulties in completing questionnaires on schedule, etc). A solution to enhance/resolve compliance should be discussed with the patient. Discussions and compliance review should be reflected in source documents.

8.1.6 Subsequent Anti-lymphoma Therapy

The following information on subsequent anti-lymphoma therapies will be collected during the study:

- Receipt of subsequent anti-lymphoma therapy
- Response to subsequent anti-lymphoma therapy

For any subsequent anti-lymphoma therapy, the start date, end date, best response, and date of best response should be documented in the appropriate section of the eCRF.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA in the relevant Module.

8.2.1 Physical Examinations

The physical examination includes, at a minimum, the general appearance of the patient, height (Screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. The lymphatic system examination will include examination of palpable lymph nodes and spleen and liver below the costal margin on the respective side. Only physicians should perform the lymphatic system examination. As much as possible, the same person should perform all the lymphatic exams for a given patient.

Physical examination will be performed at timelines as specified in the SoA in the relevant

Module. Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as adverse events, see Section 8.3.4 for details.

8.2.2 Vital Signs

Vital signs (including blood pressure, pulse, pulse oxygen saturation, and body temperature) will be assessed at timelines as specified in the SoA in the relevant Module. Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).

Vital signs will be measured in a sitting position after at least 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse. Three readings of blood pressure and pulse will be taken and should be reported in the patient notes. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the eCRF.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.5.

8.2.3 Electrocardiograms

All ECGs to be conducted as triplicate measurements, within approximately 5 minutes of starting (the 3 ECGs separated by approximately 1 minute). Assessments should be performed as close as possible to, but within 30 minutes of the nominal time point.

Triplicate 12-lead ECGs will be obtained at the time points specified in the SoA in the relevant Module.

Additional ECGs may be taken at the discretion of the investigator.

Twelve-lead ECGs will be obtained after the patient has been resting supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position. A standardised ECG machine should be used, and the patient should be examined using the same machine throughout the study, if possible.

After paper ECGs have been recorded, the investigator or designated physician will review each of the ECGs and may refer to a local cardiologist, if appropriate. A paper copy should be filed in the patient's medical records.

If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition. For all ECGs, details of

intervals PR, R-R, QRS, QT, and QTcF and an overall evaluation will be recorded (normal; abnormal, non-clinically significant or abnormal, clinically significant).

Situations in which ECG results should be reported as AEs are described in Section 8.3.5.

8.2.4 Clinical Safety Laboratory Assessments

See Table 4 for the list of clinical safety laboratory tests to be performed and the SoA in the relevant Module for the timing and frequency.

The date and time of each collection will be recorded in the appropriate eCRF.

Laboratory values that meet the criteria for CTCAE Grade 3 or have changed significantly from baseline and are considered to be of clinical concern will be repeated/confirmed within 7 days and followed up as appropriate.

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF. All patients with Grades 3 or 4 laboratory values at the time of completion or discontinuation from study treatment must be followed and have further tests performed until the laboratory values have returned to Grades 1 or 2, unless these values are not likely to improve because of the underlying disease.

Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.5.

All laboratory safety analyses, including clinical chemistry, haematology and urinalysis, will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Other safety laboratory tests include assessment for pregnancy, viral serology (HIV antibodies, CMV antibodies and hepatitis serology [hepatitis B surface antigen, hepatitis B surface antibodies, HBc antibodies, and hepatitis C virus antibodies]), and SARS-CoV-2 PCR testing and antibodies (if clinically indicated), and serum immunoglobulins (IgA, IgG, IgM). For patients with positive anti HBcAb or anti-hepatitis C Ab at screening with documented negative HBV DNA or HCV RNA, HBV DNA and/or HCV RNA PCR testing (as applicable) will be assessed every 3 months during study treatment (Table 6). Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to

48 hours).

The following laboratory variables will be measured.

Table 4 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry**
B-Haemoglobin (Hb)	S/P-Creatinine
B-Glycosylated haemoglobin (HbA1c) (fasting)	S/P-Bilirubin, total
B-Leukocyte count (WBC count)	S/P-Alkaline phosphatase
B-Leukocyte differential count	S/P-AST
Neutrophils	S/P-ALT
Lymphocytes	S/P-Albumin
Eosinophils	S/P-Potassium
B-Platelet count	S/P-Calcium, total
Urinalysis	S/P-Sodium
U-Glucose	S/P-Glucose (fasting)
U-Protein	S/P-Magnesium
U-Blood	S/P-Total protein
U-Microscopy (red blood cells and white blood cells, bacteria, casts and crystals) only perform if urinalysis is abnormal [c]	S/P-Free T4 [a]
	S/P-TSH [a]
	S/P-bicarbonate
U-pH	S/P-BUN/urea nitrogen
U-Specific gravity	S/P-chloride
U-bilirubin	S/P-LDH
U-Ketones	S/P-Phosphate
Other	S/P-Uric acid
Beta-2 microglobulin [b]	S/P-Troponin I or T [b]
	S/P-Lipids (fasting)
	S/P-Gamma-glutamyl transferase

[a] Test will only be performed on Day 1 in each cycle and when clinically indicated.
[b] At screening and then as clinically indicated.
[c] Denmark only: U-Microscopy is not required.

NB. In case a patient shows an AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix E 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

Lipids: triglycerides, high density lipoprotein, low density lipoprotein, and cholesterol.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; B: blood; BUN: blood urea nitrogen; P: plasma; S: serum; T4: thyroxine; TSH: thyroid-stimulating hormone; U: urine; ULN: upper limit of normal; WBC: white blood cell.

8.2.4.1 Glucose and HbA1c

Blood glucose and HbA1c will be assessed according to the SoA in the relevant Module. On blood glucose assessment days (incorporating clinical chemistry and glucose) it is requested that patients refrain from caloric intake for ≥ 4 hours prior to the morning dose of study treatment.

8.2.4.2 Serum Creatinine

After Cycle 2 onwards, patients taking capivasertib and metformin in combination should have creatinine assessments conducted as part of the routine clinical chemistry with additional monitoring of creatinine at the discretion of the investigator.

Patients on metformin should attend the study site for monitoring of serum creatinine at least once per week for the first 3 weeks after initiation of metformin, then every 3 weeks thereafter.

8.2.5 Other Safety Assessments

8.2.5.1 ECOG Performance Status

ECOG performance status will be assessed at the times specified in the SoA in the relevant Module. ECOG performance status is scored as follows:

0 = Fully active, able to carry out all pre-disease activities without restrictions

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)

2 = Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair

8.2.5.2 Echocardiogram / MUGA Scan

Assessments will be performed at screening and thereafter as clinically indicated.
Bi-dimensional ECHO is the preferred modality because of the global technetium [Tc-99m] shortage (but MUGA can be used alternatively).

The modality of the cardiac function assessments must be consistent within patient ie, if ECHO is used for the screening assessment and a follow-up assessment if clinically indicated, then ECHO should also be used for subsequent scans if required. The patients should also be examined using the same machine and operator whenever possible.

Situations in which ECHO or MUGA results should be reported as AEs are described in Section 8.3.5.

8.3 Adverse Events and Serious Adverse Events

The PI is responsible for ensuring that all staff involved in the study are familiar with the contents of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from time of signature of the ICF throughout the treatment period and including the follow-up period and up to 30 days after discontinuation of study treatment.

SAEs will be recorded from the time of signing of the informed consent form.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

If the investigator becomes aware of a SAE with a suspected causal relationship to the study treatment that occurs after the end of the clinical study in a patient treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs and non-serious AEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

Any AEs that are unresolved at the patient’s last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse Event Variables

'The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the study treatment(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- Seriousness criteria
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between Investigational Product and each AE and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the Investigational Product?’

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as ‘yes’.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests, vital signs, physical examinations, ECGs, and ECHO/MUGA scans will be summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, physical examinations, ECGs, and ECHO/MUGA scans should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.7 Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.3.8 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New primary cancers are those that are not the primary reason for the administration of study treatment and are identified after the patient's inclusion in this study. They do not include progression or transformation of the original cancer. Patients who develop a new cancer should be managed according to institutional guidelines with diagnostic evaluations as clinically indicated, and it may be necessary for patients to permanently discontinue study treatment. Further guidance is provided in Appendix B 2.

8.3.9 Deaths

All deaths that occur during the Treatment Period, or within the protocol-defined follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly resulting from PD should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to PD under study, the AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign the main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE and documented in the Statement of Death page in the eCRF, but every effort should be made to determine a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.

Deaths occurring after the protocol-defined follow-up period after the administration of the last dose of study treatment should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined follow-up period and the event is considered to be due to a late-onset toxicity to study treatment, then it should also be reported as an SAE.

8.3.10 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

8.3.11 Pregnancy

A pregnancy test will be administered to women of childbearing potential at Screening, on Cycle 1 Day 1, at discontinuation of study treatment, and as clinically indicated. Confirmation of absence of pregnancy is strongly recommended in case of delayed menstrual period (including infrequent or irregular menstrual cycles).

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except where the pregnancy is discovered before the study patient has received any study treatment.

8.3.11.1 Maternal Exposure

If a patient becomes pregnant during the course of the study, capivasertib should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomaly(/ies)/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.10) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

8.3.11.2 Paternal Exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 16 weeks following the last dose of capivasertib. Patients wishing to father children should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly), occurring from the date of the first dose until 16 weeks after the last dose should, if possible, be followed up and documented.

8.3.12 Medication Error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.10) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 4.

8.3.13 Adverse Events of Special Interest

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of capivasertib safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and reported as per Section 8.3.10.

A list of AESIs can be seen below:

- Hyperglycaemia
- Non-infectious diarrhoea
- Infective pneumonia
- Rash
- Stomatitis
- QT Prolongation
- Haematological effects

8.4 Overdose

There is currently no specific treatment in the event of an overdose with capivasertib and possible symptoms of overdose are not established. Capivasertib must only be used in accordance with the relevant clinical protocol. Adverse events associated with overdose should be treated in response to symptoms. Any dose, or frequency of dosing, that exceeds the dose regimen specified in the study protocol should be reported as an overdose.

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study treatment occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all

relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see section 8.3.10) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses. Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR. Anonymised samples will be retained no more than 5 years after the CSR is finalised.

8.5.1 Pharmacokinetics

- Blood samples will be collected for measurement of plasma concentrations of capivasertib as specified in the SoA in the relevant Module.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor, eg, for safety reasons.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in plasma will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Not applicable.

8.5.3 Pharmacodynamics

Not applicable.

8.6 CCI

8.6.1 CCI

CCI

- CCI
- CCI
- CCI
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8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA in the relevant Module and is subject to agreement in the ICF addendum.

CCI Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study. The saliva sample will be collected at CCI. If a sample is not collected at that time, it may be collected at any time during the study or during a separate post-study visit, if necessary.

See Appendix D for information regarding the Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

For storage and destruction of genetic samples see Appendix D.

8.8 Medical Resource Utilization and Health Economics

Not applicable.

9 STATISTICAL CONSIDERATIONS - CORE

9.1 Statistical Hypotheses

Refer to the relevant Module for information.

9.2 Sample Size Determination

Refer to the relevant Module for information.

9.3 Populations for Analyses

The following populations are defined:

Table 5 Populations for Analysis

Analysis set	Description
Enrolled	All patients who sign the ICF.
Safety	All patients who receive any amount of study treatment. Safety data will not be formally analysed but summarised using the safety analysis set.
Response evaluable	All patients, treated with study treatment, with measurable disease at baseline.
Pharmacokinetic	All patients who receive at least 1 dose of capivasertib, for whom there is at least 1 reportable PK concentration.

ICF: informed consent form; PK: pharmacokinetic(s).

9.4 Statistical Analyses

The SAP will be finalised within 90 days after First Patient In, but it will be aimed to have it finalised prior to First Patient In. It will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1 General Considerations

Analyses will be performed by AstraZeneca or its representatives, including CROs. A comprehensive SAP will be developed and will describe the patient populations to be included in the analyses, the analyses including any subgroup analyses or sensitivity analyses, and the procedures to account for missing, unused, and spurious data.

Unless stated otherwise, each Cohort will be analysed separately.

Continuous data will be summarised by the number of observations, mean, standard deviation, median, minimum and maximum. Geometric mean and coefficient of variation may be

presented as applicable. Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated from the population total. Time to event variables will be presented using the Kaplan-Meier methodology, including median time calculated from the Kaplan-Meier curves.

In general, the last observed measurement prior to first dose of study treatment will be considered the baseline measurement. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose. Assessments on the day of first dose, when neither time nor a nominal pre-dose indicator are captured, will be considered prior to first dose if such procedures are required by the protocol to be conducted before the first dose.

Depending on the extent of any impact, summaries of data relating to patients diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study treatment, and other protocol deviations) may be generated. More detail will be provided in the SAP.

The efficacy endpoints for tumour response (ORR, DoR, and TTR) will be summarised and analysed based upon the response evaluable analysis set. The efficacy endpoints for OS, PFS, and TFST, QoL, safety and treatment exposure data will be summarised based upon the safety analysis set. Pharmacokinetic data will be summarised based on the PK analysis set. Study population and demography data will be summarised based upon the safety analysis set.

Refer to the relevant Module for details on analyses and data cut-off triggers.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint(s)

ORR is defined as the proportion of patients achieving either CR or PR as assessed by BICR and will be based on the response evaluable analysis set. In addition, for sensitivity analysis purposes, ORR will also be defined as the proportion of patients achieving either CR or PR as assessed by the investigator and will be based on the response evaluable analysis set.

Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the patient withdraws from therapy. Patients who discontinue treatment without a response or progression, receive subsequent anti-lymphoma therapy and then respond will not be included as responders in the ORR.

The ORR will include data of all tumour assessments, regardless of whether it was scheduled or not.

ORR will be presented by the number and percentage of patients with a response (CR/PR)

including 95% CIs based on exact binomial proportions.

Best objective response will also be summarised by n (%) for each category, with no formal statistical analysis presented.

9.4.2.2 Secondary Endpoint(s)

Primary analysis on secondary endpoints will be based on BICR reviewed data. Sensitivity analyses will be performed based on investigator assessments.

Duration of Response (DoR)

DoR will be 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 coincide with date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit that was CR or PR.

The analysis will include all patients in the response evaluable analysis set who had a response, regardless of whether the patient withdraws from therapy.

If a patient does not progress following a response, then the censoring time will be determined by applying the same censoring rules as applied for PFS.

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

Progression-Free Survival (PFS)

The PFS is defined as the time from date of first dose to date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from treatment or receives another anti-lymphoma therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable assessment. The PFS time will always be derived based on scan/assessment dates and not on visit dates.

Kaplan-Meier plots of PFS will be presented. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (progression or death) will be provided along with the median PFS, its 95% CI, and the proportion of patients who were progression free at 6 months, 12 months, and 18 months.

The treatment status at progression of patients at the time of analysis will be summarised. This will include the number and percentage of patients who were on treatment at the time of

progression, the number and percentage of patients who discontinued study treatment prior to progression, the number and percentage of patients who have not progressed and were on treatment or discontinued treatment. This will also provide a distribution of number of days prior to progression for the patients who have discontinued treatment.

Overall Survival (OS)

The OS is defined as the time from date of first dose until death due to any case regardless of whether patient withdraws from treatment or receives another anti-lymphoma therapy. Any patient not known to have died at the time of analysis will be censored on the last recorded date on which the patient was known to be alive.

Note: Survival follow-up phone calls will be made in the week following the date of DCO for the analysis, if patients are confirmed to be alive or if the death date is after the DCO date these patients will be censored at the date of DCO.

Overall survival data will be presented similarly to the presentation described for PFS.

Time to First Subsequent Therapy or Death (TFST)

Time to first subsequent anti-lymphoma therapy or death is defined as time from date of first dose until the start date of subsequent anti-lymphoma therapy or death due to any cause and will include all dosed patients regardless of whether the patient withdraws from therapy, receives another anti-lymphoma therapy or clinically progresses prior to progression according to the Lugano 2014 Classification for NHL.

Time to first subsequent anti-lymphoma therapy or death data will be presented similarly to the presentation described for PFS.

Time to Objective Response (TTR)

Time to objective response is defined as the time from date of first dose until the date of first documented objective response and will include all patients in the response evaluable analysis set who had a response.

The TTR will be summarised (ie, number of patients [%] based upon the number of responders] by scheduled assessment time point that the response was first observed. Additionally, descriptive summary statistics will also be presented. Associated Kaplan-Meier curves may also be presented.

9.4.3 Safety

Safety analyses will be performed using the safety analysis set. Safety data will be presented using descriptive statistics unless otherwise specified.

9.4.3.1 Adverse Events

Adverse events will be coded using the most recent version of MedDRA that will have been released for execution at AstraZeneca/designee.

Adverse events will be presented by SOC and/or PT, covering number and percentage of patients reporting at least one event and number of events where appropriate.

Only treatment-emergent AEs will be presented. Adverse events occurring prior to start of study treatment and post-treatment AEs will only be listed.

An overview of AEs will present the number and percentage of patients with any AE, AEs with outcome of death, SAEs, and AEs leading to discontinuation of treatment, AESIs, as well as AEs leading to withdrawal from study, as well as the number of individual occurrences in these categories.

Separate AE tables will be provided taking into consideration relationship as assessed by the investigator, maximum CTCAE grading, seriousness, death and events leading to discontinuation of treatment as well as other action taken related to treatment, events of special interest, other significant AEs and timing of events.

An additional table will present number and percentage of patients with most common AEs. Most common (eg, frequency of > x%, ≥ x%) will be defined in the SAP.

Key patient information will be presented for patients with AEs with outcome of death, SAEs, AEs leading to discontinuation of treatment and AEs leading to treatment delay.

An AE listing for the safety analysis set will cover details for each individual AE.

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to treatment discontinuation. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

Treatment emergent AE

The following events are considered treatment emergent:

- AEs with an onset date on or after the first dose of study treatment and within 30 days after last dose of study treatment or up to the day prior to start of subsequent therapy, whichever comes first.
- Worsening of pre-existing events on or after first dose of study treatment and within 30 days after last dose of study treatment or up to the day prior to start of subsequent therapy.

Full details of AE analyses will be provided in the SAP.

9.4.3.2 Other Safety Endpoint(s)

Full details of the analysis of safety data will be provided in the SAP.

Exposure

Duration of exposure will be summarised appropriately.

Laboratory Safety Variable

For each scheduled post-baseline visit, descriptive statistics for all clinical chemistry and haematology parameters will be presented for observed values and change from baseline.

A shift table presenting number of patients with their laboratory status (eg, low, normal, high, or CTCAE grades) from baseline to maximum and minimum on-treatment values will be provided.

Elevation in liver parameters for assessments of Hy's Law will be done and reported appropriately if potential cases have been identified during the course of the study.

Key patient information will be presented for patients with treatment-emergent changes in laboratory parameters outside of predefined criteria.

A frequency table of urinalysis presenting the number of patients reporting at least one treatment-emergent increase in baseline category will be provided. A shift table for urinalysis presenting the baseline assessment against the maximum on-treatment category will also be provided.

Supportive laboratory listings covering observed values and changes from baseline for each individual patient as well as abnormalities will be presented.

Details of analyses of laboratory safety variables will be provided in the SAP.

Vital Signs

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline.

A shift table presenting number of patients with their abnormality status (eg, low, normal, high,) from baseline to maximum and minimum on-treatment values will be provided.

Key patient information will be presented for patients with treatment-emergent changes in vital signs outside of predefined criteria.

Supportive vital sign listings covering observed values and changes from baseline as well as abnormalities will be provided.

Details of vital signs analyses, including definition of abnormality criteria (eg, definition of low, normal, high) and project specific criteria for treatment-emergent changes in vital signs parameters will be provided in the SAP.

Electrocardiogram

For each scheduled post-baseline assessment, descriptive statistics for all ECG parameters will be presented for observed values and change from baseline.

Uncorrected QT interval results will be corrected according to the Fridericia's formula.

For QTcF a frequency table presenting number of patients with values exceeding thresholds of 450 ms, 480 ms and 500 ms at any time during the treatment will be provided. Similarly, number of patients with change from baseline in QTcF exceeding 30 ms, 60 ms and 90 ms at any time during the treatment, as well as the combination of thresholds on observed values and change from baseline values will be provided.

A table presenting the interpretation of the ECG reading (normal, abnormal) at baseline and last assessment on treatment will be provided, including shifts in interpretation as compared to baseline.

Key patient information will be presented for patients with treatment-emergent ECG values outside of predefined criteria.

Supportive ECG listings covering observed values and change from baseline for each patient will be presented.

Details of ECG analyses, including definition of reference values and abnormalities will be provided in the SAP.

Death

Details of any death will be listed for all patients.

9.4.4 Other Analyses

9.4.4.1 Pharmacokinetics

Pharmacokinetic analyses will be performed based on the PK analysis set. Any exclusion of data will be documented and justified.

The plasma concentration-time data will be analysed by population PK methods using non-linear mixed-effects modelling. Pharmacokinetic parameters, including variability parameters, will be estimated as data permits. The influence of intrinsic (eg, ethnicity, gender, age, weight, renal function, and hepatic function) and extrinsic (eg, concomitant medication) factors will be evaluated.

Details will be outlined in a separate modelling analysis plan finalised before database lock and results may be reported separately.

Data from this study may be pooled with data from other capivasertib studies.

9.4.4.2 Patient-reported Outcomes (PROs)

Patient-reported outcome data from the EORTC QLQ-C30, CCI , PRO-CTCAE, patient reported anti-diarrhoeal medication, PGI-TT, CCI will be analysed by descriptive summaries and graphical presentations. The analysis will be based on the all dosed patients.

The actual value and change from baseline in each of the functional scales, symptom scales and global health status/QoL scores in EORTC QLQ-C30 will be summarised descriptively at each time point in each cohort.

PRO-CTCAE, PGI-TT and patient-reported anti-diarrhoeal medication data will be summarised descriptively over time in each cohort, including the proportion of patients reporting different levels of each symptomatic AEs, overall side effects burden and anti-diarrhoeal medication use.

CCI

CCI

The compliance of each PRO questionnaires will also be summarised.

The clinically meaningful change in EORTC QLQ-C30 subscale scores will be explored using anchor-based methods and distribution-based methods. Time to deterioration and proportion of patients with deteriorated, stable and improved scores in EORTC QLQ-C30 subscales will also be explored. Additional analyses for PRO-CTCAE data and other PRO measures may also be considered.

Further details will be included in the SAP.

9.4.5 Exploratory Analyses

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Data from this study may be pooled with data from other capivasertib studies.

9.5 Interim Analyses

Interim analyses will be conducted separately for each Module and are described in the relevant Module.

9.6 Data Monitoring Committee

This study will have a Study Steering Committee (SSC). The details of the roles and responsibilities of the SSC are provided in a charter separate from the Core Protocol (see also Appendix A 5). The SSC will be reviewing safety data approximately every 6 months and additional SSC review may be triggered in case of significant new safety findings. A Safety

Review Committee may be established in case a module evaluating capivasertib in combination with other agents is added in the future.

MODULE 1 – CAPIVASERTIB MONOTHERAPY IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN LYMPHOMA

10 INTRODUCTION - MODULE 1

10.1 Module Summary – Module 1

10.1.1 Schedule of Activities – Capivasertib Monotherapy

The SoAs for Module 1 are presented in Table 6 (Screening and Treatment Period) and Table 7 (Follow-up Period).

Table 6 Schedule of Activities (Screening and Treatment Period) – Module 1: Capivasertib Monotherapy

Study Cycles (28-Day)	Screening [a]	Treatment Period													Notes	Details in CSP Section or Appendix
		Cycle 1				Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6	Cycles 7-12	Cycle ≥ 13 [b]		
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		
Visit Window			**±2 d**										**±7 d**			
Informed consent	X															Appendix A 3
Inclusion and exclusion criteria	X															5.1; 5.2;13.1; 13.2
Demography	X															5.1
Medical history	X															5.1
Disease characteristics [c]	X															5.1
Disease prognostic scores	X															8, Appendix J
Previous anti-lymphoma therapies	X															5.1
Physical examination [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	C1D1: Pre-dose; C1D15: post dose; Pre-dose at all other visits	8.2.1
Height	X															8.2.1
Weight	X	X				X		X		X	X	X	X	X		8.2.1
Vital signs [d,e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Pre-dose	8.2.2
ECOG performance status [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.2.5.1
12-lead ECG (triplicate) [f]	X	X				X		Pre-dose C3D1 and every 12 weeks thereafter, and as clinically indicated							C1D1: (Pre-dose and 1 to 2 h post dose)	8.2.3
ECHO/MUGA	At Screening and as clinically indicated															8.2.5.2

Study Cycles (28-Day)	Screening [a]	Treatment Period													Notes	Details in CSP Section or Appendix
		Cycle 1				Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6	Cycles 7-12	Cycle ≥ 13 [b]		
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		
Visit Window			**±2 d**										**±7 d**			
Brain MRI/CT scan [g]	Only if clinically indicated															8.1.2
Fresh or archival tumour sample [h, r]	X														When available (eg, at relapse)	8.6.1
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.3
Concomitant medication and non-drug therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X		6.5
Study treatment																
Capivasertib dispensation		X				X		X		X	X	X	X	X		6
Capivasertib intake		BD 4 days on / 3 days off in each week of a 28-day cycle until PD or unacceptable toxicity														6.1
Capivasertib treatment compliance [i]		X	X	X	X	X	X	X	X	X	X	X	X	X		6.4
Laboratory assessments																
Pregnancy test (WOCBP)	X (serum)	Urine pregnancy tests pre-dose on C1D1 and as clinically indicated														8.2.4
Haematology [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.2.4
Clinical chemistry [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	C1D1: pre-dose and 1 to 2 h post-dose	8.2.4
Viral serology [j]	X	For patients with positive anti HBcAb or anti-HCV Ab at screening, HBV DNA or HCV RNA every 3 months from C1D1														8.2.4
SARS-CoV-2	X	As clinically indicated														8.2.4
Urinalysis [d]	X	X		X		X		X		X	X	X	X	X		8.2.4

Study Cycles (28-Day)	Screening [a]	Treatment Period													Notes	Details in CSP Section or Appendix
		Cycle 1				Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6	Cycles 7-12	Cycle ≥ 13 [b]		
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		
Visit Window			**±2 d**										**±7 d**			
Serum IgA, IgG, IgM		X						X					X (C7 only)			8.2.4
HbA1c (fasted)	X	Every 12 weeks starting from C1D1 and as clinically indicated														8.2.4
Serum glucose (fasted) [k]	X	Pre-dose and 4 hours post-dose on C1D1. Pre-dose only at Day 1 of each subsequent cycle and as clinically indicated														8.2.4
Serum lipids (fasted)	X	Every 12 weeks starting from C1D1 and as clinically indicated														8.2.4
Tumour Assessments																
CT scan [l]	X	Weeks 8, 16, 24, 36, 48, and 60 and thereafter every 24 weeks for FL/MZL and every 12 weeks for MCL, until disease progression													Window for CT scan: ± 7 days	8.1.2
PET scan [n]	X	Week 8, 16, and 24 and thereafter to confirm CR or as clinically indicated [m]													Window for PET scan: ± 7 days	8.1.2
Bone marrow (biopsy or aspirate) [o]	X							To confirm CR (if prior bone marrow involvement) and as clinically indicated								8.1.1
Response assessment Lugano 2014 Classification		Weeks 8, 16, 24, 36, 48, and 60 and thereafter every 24 weeks for FL/MZL and every 12 weeks for MCL, or as clinically indicated until radiological PD													Window for response assessment: ± 7 days	8.1.3.1
B symptoms	X	At every tumour assessment scan														8.1.4.3
Endoscopy/ histology	X (as clinically indicated)	To confirm CR (if prior gastrointestinal involvement), and as clinically indicated														8.1.4.1

Study Cycles (28-Day)	Screening [a]	Treatment Period													Notes	Details in CSP Section or Appendix
		Cycle 1				Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6	Cycles 7-12	Cycle ≥ 13 [b]		
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		
Visit Window			±2 d										±7 d			
Pharmacokinetic Assessments																
Blood sample for plasma PK		X	X	X	X										D1: 1 h (+15 min), 2 h (+15 min) and 4 h (+30 min) post-dose Predose (-90 min to 0 min) on D8, 15 and 22	8.5.1
Exploratory and CCI Assessments																
CCI [r]	X	X		X		X	X	At every tumour assessment scan							Samples collected pre-dose	8.6.1
CCI [r]	X	X		X		X	X	At every tumour assessment scan							Samples collected pre-dose	8.6.1
CCI [p, r]	X	X		X		X	X	At every tumour assessment scan							Samples collected pre-dose	8.6.1
CCI [q, r]	X	X		X		X	X	At every tumour assessment scan							Samples collected pre-dose	8.6.1
CCI [r]		X													Pre-dose; if not collected at C1D1, may be collected at any time during the study, or during a separate post-study visit, if necessary	8.7, Appendix D

Study Cycles (28-Day)	Screening [a]	Treatment Period													Notes	Details in CSP Section or Appendix
		Cycle 1				Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6	Cycles 7-12	Cycle ≥ 13 [b]		
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		
Visit Window			**±2 d**										**±7 d**			
PRO collection																
Prepare ePRO device and train patient		X														8.1.5
EORTC QLQ-C30		C1D1 and every 4 weeks from C1D1 for the first 24 weeks and then every 12 weeks thereafter until 12 weeks post progression														8.1.5.1, Appendix K 1
CCI		C1D1 and every 12 weeks from C1D1 for the first 24 weeks														8.1.5.2, Appendix K 2
PRO-CTCAE		C1D1, every week from C1D1 for the first 4 weeks, every 4 weeks for the next 8 weeks (ie, at Week 8, Week 12), and every 12 weeks afterwards until EOT														8.1.5.3, Appendix K 3
Patient-reported anti-diarrhoeal medication		C1D1, every week from C1D1 for the first 4 weeks, every 4 weeks for the next 8 weeks (ie, at Week 8, Week 12), and every 12 weeks afterwards until EOT														8.1.5.4, Appendix K 4
PGI-TT		C1D1, every week from C1D1 for the first 4 weeks, every 4 weeks for the next 8 weeks (ie, at Week 8, Week 12), and every 12 weeks afterwards until EOT														8.1.5.5, appendix K 5
CCI		C1D1, every 4 weeks from C1D1 for the first 24 weeks and then every 12 weeks thereafter until 12 weeks post progression														8.1.5.6, Appendix K 6
CCI		Every 12 weeks from C1D1 for the first 24 weeks														8.1.5.7, Appendix K 7
CCI		C1D1 and every 12 weeks from C1D1 until 12 weeks post progression														8.1.5.8, Appendix K 8

[a] Screening tests should be performed within 28 days before the first administration of capivasertib, unless otherwise indicated.

[b] Treatment with capivasertib may be continued for as long as there is no PD or unacceptable toxicity. In the case of a capivasertib dosing delay at the beginning of the cycle, the same routine safety measurements and routine clinical procedures must be repeated on the next planned date of dosing. Cycles are 28 days long.

[c] Including also disease stage (I, II, III, IV) and extent (S [splenic involvement], E [extranodal disease], X [bulky disease], bone marrow involvement) as determined by the investigator at screening.

[d] Unscheduled assessments are allowed as clinically indicated.

[e] Vital signs (blood pressure, pulse, pulse oxygen saturation, and body temperature) will be assessed after the patient has rested in the sitting position for ≥ 5 minutes.

[f] 12-lead ECG will be done in triplicate (≥ 1 minute apart) at screening. The calculated QTc average of the 3 ECGs must be < 470 ms for eligibility. Patients should be in supine position and resting for at least 10 minutes before study-related ECGs.

[g] Brain imaging (MRI with contrast preferred) will be performed at screening only if there is a prior history of CNS involvement or if there are neurologic signs or symptoms present or as clinically indicated during the study.

[h] CCI [redacted]

[i] Patients will receive a drug diary to record the specific time each dose was taken and to record reasons for any missed doses. Compliance will be assessed at each study visit.

[j] Viral serology will include HIV antibodies, CMV antibodies and hepatitis serology. Hepatitis serology must include hepatitis B surface antigen, hepatitis B surface antibodies, hepatitis B core antibodies, and HCV antibodies. In addition, any patients testing positive for any hepatitis serology, must have PCR testing for verification purposes.

[k] Pre-dose glucose samples must be collected under fasting conditions (no caloric intake for ≥ 4 hours). Post-dose glucose samples can be collected under fasting or non-fasting conditions.

[l] If IV contrast is contraindicated, an MRI can be performed.

[m] Once the first complete metabolic response has been documented, subsequent follow-up with CT with IV contrast only. Unscheduled PET/CT scans can be done if clinically indicated (eg, suspicion of PD). Patients who discontinue treatment prior to PD should continue to be scanned until progression.

[n] For MZL patients with no FDG-avid disease at baseline, only CT with IV contrast will be used for disease response assessment.

[o] CCI [redacted] is done as part of routine clinical practice, samples can be collected for CCI [redacted]

[p] CCI [redacted]

[q] CCI [redacted]

[r] Central laboratory collection.

C: cycle; CR: complete response; CSP: Clinical Study Protocol; CT: computed tomography; CCI [redacted]; d/D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; CCI [redacted]; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer quality of life questionnaire Core 30; EOT: end of treatment; ePRO: electronic patient-reported outcome; CCI [redacted]; FLIPI: Follicular Lymphoma International Prognostic Index; HbA1c: glycosylated haemoglobin; HBV: hepatitis B virus; HCV: hepatitis C virus; Ig: immunoglobulin; IV: intravenous; LTFU: long-term follow-up; MCL: mantle cell lymphoma; MIPI: Mantle Cell Lymphoma International Prognostic Index; CCI [redacted]; MRI: magnetic resonance imaging; MUGA: multiple-gated acquisition; NK: natural killer; PCR: polymerase chain reaction; PD: progression of disease; PET: positron emission tomography; CCI [redacted]; CCI [redacted]; PGI-TT: Patient Global Impression of Treatment Tolerability; PK: pharmacokinetics; PRO: patient-reported outcome; PRO-CTCAE: National Cancer Institute patient-reported outcomes Common Terminology Criteria for Adverse Events; QTc: corrected QT interval; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; WOCBP: woman of childbearing potential.

Table 7 Schedule of Activities (Follow-up Period) – Module 1: Capivasertib Monotherapy

Study Cycles (28-Day)	Follow-up Period			Notes	Details in CSP Section or Appendix
	EOT [a]	Post-treatment follow-up	LTFU [b]		
Study Day		**30 days after last dose**	**Every 12 weeks**		
Visit Window		**±7 d**			
Physical examination [c]	X	X			8.2.1
Weight	X	X			8.2.1
Vital signs [c,d]	X	X			8.2.2
ECOG performance status [c]	X				8.2.5.1
12-lead ECG (triplicate) [e]	X	X			8.2.3
ECHO/MUGA	X	As clinically indicated			8.2.5.2
Fresh or archival tumour sample [f, j]	X (optional at progression)			Unscheduled tumour biopsies may be submitted to central laboratory if available	8.6.1
Adverse events	X	X	X [g]		8.3
Concomitant medication and non-drug therapies	X	X	X [h]		6.5
Laboratory assessments					
Pregnancy test (WOCBP)	X (urine)	X (urine)			8.2.4
Haematology [c]	X	X			8.2.4
Clinical chemistry [c]	X	X			8.2.4
Urinalysis [c]	X	X			8.2.4
Serum IgA, IgG, IgM	X				8.2.4
HbA1c (fasted)	X				8.2.4
Serum glucose (fasted)	X	X			8.2.4
Serum lipids (fasted)	X	X			8.2.4

Study Cycles (28-Day)	Follow-up Period			Notes	Details in CSP Section or Appendix
	EOT [a]	Post-treatment follow-up	LTFU [b]		
Study Day		**30 days after last dose**	**Every 12 weeks**		
Visit Window		**±7 d**			
Tumour Assessments					
Subsequent anti-lymphoma therapies		X			8.1.6
Survival status			X [b]		
Response assessment Lugano 2014 Classification		X [i]		For patients who stop study treatment without PD	8.1.3.1
Exploratory and CCI Assessments					
CCI [j]	X				8.6.1
CCI [j]	X				8.6.1
CCI [j]	X				8.6.1
CCI [j]	X				8.6.1
PRO collection					
EORTC QLQ-C30	X	Every 12 weeks until 12 weeks post progression			8.1.5.1, Appendix K 1
CCI	X				8.1.5.2, Appendix K 2
PRO-CTCAE	X	X			8.1.5.3, Appendix K 3
Patient-reported anti-diarrhoeal medication	X	X			8.1.5.4, Appendix K 4
PGI-TT	X	X			8.1.5.5, Appendix K 5
CCI	X	Every 12 weeks after EOT until 12 weeks post progression			8.1.5.6, Appendix K 7
CCI	X	Every 12 weeks after EOT until 12 weeks post progression			8.1.5.8, Appendix K 8

[a] End of treatment visit is for patients who permanently discontinue study intervention for any reason, including disease progression (except for death, lost to follow-up or withdrawal of consent). The EOT visit should be performed within 7 days of the last dose of study intervention, if possible, and is not required for patients who discontinue from study intervention within 10 days of a scheduled study visit or if the EOT visit would be performed within 14 days of the post-treatment follow-up visit.

[b] Patients who progress or start alternative anti-lymphoma therapy will be contacted approximately every 12 weeks (± 7 days) by study site visit or telephone, to assess survival, drug-related SAEs, concomitant medication and non-drug therapies related to the management of drug-related SAEs, and the use of alternative anti-lymphoma therapy until death or lost to follow-up, unless they have withdrawn consent.

[c] Unscheduled assessments are allowed as clinically indicated.

[d] Vital signs (blood pressure, pulse, pulse oxygen saturation, and body temperature) will be assessed after the patient has rested in the sitting position for ≥ 5 minutes.

[e] Patients should be in supine position and resting for at least 10 minutes before study-related ECGs.

[f] For patients with involved bone marrow, a bone marrow biopsy is acceptable.

[g] Collection of drug-related SAEs only.

[h] Collection of concomitant medication and non-drug therapies related to the management of drug-related SAEs only.

[i] Patients who discontinue study treatment for reasons other than PD will continue to be scanned for disease response until documented PD and regardless of starting a new anti-lymphoma therapy following the tumour assessment schedule detailed in the SoA for Screening and Treatment Period (Table 6), ie, every 8 weeks (± 7 days) until Week 24 (ie, Weeks 8, 16, and 24), every 12 weeks (± 7 days) until Week 60 (ie, Weeks 36, 48 and 60) and thereafter every 12 weeks (± 7 days) for R/R MCL and every 24 weeks (± 7 days) for R/R FL/MZL.

[j] Central laboratory collection.

CSP: Clinical Study Protocol; CCI [redacted]; d/D: day; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; CCI [redacted]; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer quality of life questionnaire Core 30; EOT: end of treatment; CCI [redacted]; HbA1c: glycosylated haemoglobin; Ig: immunoglobulin; LTFU: long-term follow-up; CCI [redacted]; MUGA: multiple-gated acquisition; PD: progression of disease; CCI [redacted]; PGI-TT: Patient Global Impression of Treatment Tolerability; PRO: patient-reported outcome; PRO-CTCAE: National Cancer Institute patient-reported outcomes Common Terminology Criteria for Adverse Events; SAE: serious adverse event; WOCBP: woman of childbearing potential.

10.2 Rationale for Module 1

The overall rationale for investigating capivasertib in B-cell NHL is presented in Section 2.1 of the Core Protocol. Module 1 Cohorts 1A, 1B, and 1C plan to investigate the safety and efficacy of capivasertib monotherapy in patients with R/R B-cell NHL.

10.3 Background – Module 1

10.3.1 Cohort 1A – Therapeutic Options for R/R Follicular Lymphoma

Follicular lymphoma is the most frequent subtype of indolent NHL and accounts for approximately 20% of all NHLs. This histology is further divided into 3 different grades (Grades 1 to 3) reflecting the heterogeneity in the biology of the disease. Although median OS is > 15 years, FL remains an incurable disease in most of the patients exhibiting a relapsing and remitting pattern. Median PFS progressively shorten over time with each subsequent line of therapy beyond the first (eg, 18, 9.6, 8.2 and 8.1 months after second, third, fourth, and ≥ fifth lines of therapy respectively), highlighting a clear unmet need for R/R patients (Link et al 2019).

The management of R/R disease include anti-CD20 based chemo-immunotherapy, autologous HSCT and chemo-free options such combination of lenalidomide and rituximab, PI3K inhibitors, and tazemetostat. Three PI3K inhibitors (idelalisib, duvelisib, copanlisib) have been approved for use in the US (only 1 in Europe, idelalisib) in FL that relapsed after at least 2 prior systemic therapies based on single-arm, Phase II studies. In idelalisib-treated FL patients, ORR was 56%, while median PFS was 11.0 months (Salles et al 2018). In copanlisib-treated FL patients, ORR was 59% and median DoR was 12.2 months (ALIQOPA USPI). In duvelisib-treated FL patients, ORR was 42% (CR 1%), and median DoR was 10 months (Flinn et al 2019). However, the associated safety profile (in particular, life-threatening infections, pneumonitis, transaminitis, colitis) together with their schedule of administration (eg, IV use for copanlisib) often hampers their extensive use in clinical practice. Recently, the EZH inhibitor tazemetostat has been approved based on an open-label Phase II trial. In patients with EZH2mut disease, ORR was 69% with a median DoR of 10.9 months and a median PFS of 13.8 months. In patients with wild-type EZH2, the ORR was 35%, median DoR was 13 months and median PFS was 11.1 months (Morschhauser et al 2020).

10.3.2 Cohort 1B – Therapeutic Options for R/R Marginal Zone Lymphoma

Marginal zone lymphomas represent the second most common subtype of indolent lymphoma accounting for 5-15% of NHL, although individually the 3 variants – nodal MZL, splenic MZL and extranodal MZL of mucosa-associated lymphoid tissue lymphoma (Sehn 2016). For patients with MZL relapsing disease after at least one CD20-based FDA-approved chemotherapy-free options include the BTK inhibitor ibrutinib (approved in MZL on the basis of Study 1121, a phase II trial showing ORR of 46%, CR of 3% [IMBRUVICA USPI]) and combination of lenalidomide and rituximab for patients after > 1 line of treatment of

lenalidomide (REVLIMID SmPC). However, in a post-hoc analysis in MZL subset, despite the ORR higher in lenalidomide and rituximab combination vs rituximab monotherapy (64% vs 44%) no PFS improvement was observed in this cohort compared to other histologies (Leonard et al 2019).

10.3.3 Cohort 1C – Therapeutic Options for R/R Mantle Cell Lymphoma

Mantle cell lymphoma is considered an aggressive lymphoma representing 5% to 7% of NHL and it's defined by the translocation (11;14)(q13;q32) and resulting in constitutive overexpression of cyclin D1. PI3K-dependent AKT activation leads to inhibition of glycogen synthase kinase 3β, which, when activated, phosphorylates cyclin D1, triggering its nuclear export and proteasomal degradation (VanArsdale et al 2015). Constitutive activation of PI3K in MCL alters CD1d-mediated antigen processing and presentation, ultimately resulting in decreased anti-tumour NKT cell responses. MCL is a heterogeneous disease with variable presentations, clinical and biologic risk factors, and treatment approaches. (Maddocks 2018) that often respond well in the frontline setting with combination chemotherapy, although the responses are often not durable with a median PFS after second, third, fourth, and ≥ fifth lines of therapy of 14, 6.5, 5, and 3.3 months, respectively (Kumar et al 2019). Treatment options for R/R MCL include the BTK inhibitors ibrutinib and acalabrutinib; bortezomib, lenalidomide with or without rituximab, and brexucabtagene autoleucel (IMBRUVICA USPI; CALQUENCE USPI; VELCADE USPI; REVLIMID USPI;TECARTUS USPI). Although the response rates with single-agent BTK inhibitors are relatively high, approximately one-third of patients display primary resistance to BTK inhibitors, and nearly all patients eventually progress. The outcomes of patients who progress following BTK inhibitors are relatively poor with an ORR ranging between 25% and 42% and median OS between 6 and 10 months with salvage therapies (Martin et al 2016; Epperla et al 2009; Jain et al 2018).

Recently, brexucabtagene autoleucel, a CD19-directed CAR-T therapy has been approved for R/R MCL failing ≥ 2 lines of systemic therapy including a BTK inhibitor, showing an ORR of 85% and a 12-month PFS and OS of 61% and 83%, respectively (Wang et al 2020).

Promising data from CAR-T therapies and bi-specifics antibody have also recently emerged in the landscape of indolent and aggressive lymphomas. However, toxicities related to fatal cases of cytokine release syndrome / neurotoxicity and costs should be taken into account in the treatment choice for R/R patients in future. In particular, for older patients and for those with co-morbidities that preclude aggressive treatment and for whom dependence on hospitals for infusional therapies represents a significant challenge, are likely to benefit greatly from oral monotherapy (Flinn et al 2019).

10.4 Benefit/Risk Assessment

See Section 2.3 of the Core Protocol, for an overall benefit-risk assessment for capivasertib.

11 OBJECTIVES AND ENDPOINTS – MODULE 1

See Section 3 of the Core Protocol.

12 STUDY DESIGN – MODULE 1

Module 1 is to be used in conjunction with the Core Protocol for the conduct of the study. This Module contains information required for investigators to conduct the study of capivasertib monotherapy in patients with FL, MZL, and MCL.

This Module includes 3 cohorts:

- Cohort 1A: capivasertib monotherapy in patients with R/R FL
- Cohort 1B: capivasertib monotherapy in patients with R/R MZL
- Cohort 1C: capivasertib monotherapy in patients with R/R MCL

Capivasertib will be taken at 480 mg orally BD 4 days on/3 days off until disease progression unless there is evidence of unacceptable toxicity or if the patient/investigator requests to stop the treatment.

Module 1 for capivasertib monotherapy will include:

- A Screening Period of 28 days
- A Treatment Period comprised of 28-day treatment cycles, during which patients will receive study treatment.
- A Follow-up Period which includes:
  - An EOT visit to be conducted within 7 days after discontinuation of study treatment.
  - A post-treatment follow-up visit to be conducted 30 days (± 7 days) after last dose of study treatment.
  - A LTFU Period including collection of subsequent anti-lymphoma therapy, drug-related SAEs, concomitant medication and non-drug therapies related to the management of drug-related SAEs, and survival will be assessed every 12 weeks (± 7 days) and response assessments for patient who stop study treatment without PD.

A total of 272 patients will be enrolled:

- 94 patients in Cohort 1A
- 94 patients in Cohort 1B
- 84 patients in Cohort 1C

An interim analysis focusing on safety will be conducted when approximately 30 patients across the three cohorts have had the opportunity to be treated for 8 weeks and may inform preliminary efficacy based on Investigator-assessed ORR.

An interim analysis bridging Cohorts 1A and 1B will be performed for efficacy, based on BICR, after a total of n = 28 patients in Cohort 1A plus Cohort 1B have had the opportunity to be treated for 4 months.

An interim analysis for efficacy, based on BICR, will be performed after n = 24 patients in Cohort 1C have had the opportunity to be treated for 4 months.

Enrolment will not pause whilst awaiting the interim data analysis. Additional details on the interim analyses will be provided in the SAP.

12.1 Justification for Dose

Oral capivasertib 480 mg BD given intermittently (4 days on/3 days off) is the recommended Phase II dose regimen for monotherapy. This corresponds to the maximum tolerated dose.

Although in the dose-escalation Phase I study (Banerji et al 2018) in patients with solid tumours, capivasertib 480 mg BD given intermittently (4 days on/3 days off) was defined as the maximum tolerated dose for the intermittent schedule 4 days on/3 days off, the selection of recommended Phase 2 dose for monotherapy trials, including CAPITAL, considered not only safety and long-term tolerability, but also evidence of target engagement and PK/PD relationships.

Following assessment of the multiple dosing regimens explored (either continuous or intermittent schedules), capivasertib 480 mg BD given intermittently (4 days on/3 days off) was considered the optimal balance between tolerability and efficacy. Refer to the current capivasertib IB for details.

The following evidences support the choice of the starting dose in the CAPITAL study and provide a justification of the selected intermittent schedule.

- Better long-term tolerability compared to other tested schedules (Banerji et al 2018).
- Significant biological activity as shown by target engagement/inhibition (Robertson et al 2020).
- Well-characterized and manageable safety profile based on wide clinical experience to date (refer to the current capivasertib IB), with similar clinical behaviour and PK/PD profiles both in Western and Asian population (Tamura et al 2016).

12.2 End of Study Definition

See Section 4.4 of the Core Protocol for end of study definition.

For the purpose of the primary analysis for each cohort, the DCO will be after all patients treated with capivasertib in that cohort have had the opportunity to be treated for 6 months. At the time of this DCO, the data analysis will be performed, and a cohort-specific CSR may be written.

After the primary DCO, efficacy and safety data will continue to be collected.

The DCO for the final analysis for each cohort will occur approximately 18 months after the last patient treated with capivasertib has been enrolled in the cohort or when 70% of patients have progressed or died (due to any reason) in the cohort, whichever occurs first.

Additional OS follow-up analyses may be performed separately for each cohort after the final analysis, until 70% of the patients treated with capivasertib have died due to any cause.

13 STUDY POPULATION – MODULE 1

13.1 Inclusion Criteria

In addition to meeting all core inclusion criteria (Section 5.1), patients are eligible to be included in the study cohort only if all of the following cohort-specific criteria apply.

13.1.1 Additional Inclusion Criteria for Cohort 1A (R/R FL)

1 Histologically confirmed diagnosis of FL Grade 1, 2, or 3a as assessed by investigator or local pathologist.

2 Current need for systemic treatment based on the Investigator's opinion.

3 Relapsed, progressed, or refractory (defined as failure to achieve at least a PR) after at least 2 prior systemic lines of therapy (including anti-CD20mAb and an alkylating agent).

— The treating physician should discuss with the patient all available treatment options, including the use of CAR-T cell therapy, evaluating benefits and risks before considering enrolment in this study.

4 This criterion was removed in Amendment 03; refer to Protocol Amendment Summary of Changes Table for more information.

5 Bi-dimensionally measurable disease on cross sectional imaging by CT or MRI with at least one nodal lesion > 1.5 cm in the long axis or at least one extranodal lesion > 1 cm in long axis.

13.1.2 Additional Inclusion Criteria for Cohort 1B (R/R MZL)

1 Histologically confirmed MZL including splenic, nodal, and extranodal subtypes as assessed by investigator or local pathologist.

2 Current need for systemic treatment based on the Investigator's opinion.

3 Relapsed, progressed or refractory (defined as failure to achieve at least a PR) after at least 2 prior systemic lines of therapy (including at least one anti-CD20mAb directed regimen either as monotherapy or as chemoimmunotherapy; *Helicobacter pylori* eradication and radiation therapy alone will not be considered a systemic treatment regimen).

4 This criterion was removed in Amendment 03; refer to Protocol Amendment Summary of Changes Table for more information.

5 Bi-dimensionally measurable disease on cross sectional imaging by CT or MRI with at least one nodal lesion > 1.5 cm in the long axis or at least one extranodal lesion > 1 cm in long axis.

13.1.3 Additional Inclusion Criteria for Cohort 1C (R/R MCL)

1 Histologically confirmed MCL, with documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1, as assessed by investigator or local pathologist.

2 Relapsed, progressed, or refractory (defined as failure to achieve at least a PR) after at least 2 prior systemic lines of therapy.

3 Patients must have received as prior therapies:

- BTK inhibitor and
- Anti-CD20mAb therapy.

  The treating physician should discuss with the patient all available treatment options, including the use of CAR-T cell therapy, evaluating benefits and risks before considering enrolment in this study.

4 Bi-dimensionally measurable disease on cross sectional imaging by CT or MRI with at least one nodal lesion > 1.5 cm in the long axis or at least one extranodal lesion > 1 cm in long axis.

5 South Korea Only: In the case of patients with MCL, eligibility is limited to cases where there is no beneficial treatment available in South Korea.

13.2 Exclusion Criteria

The additional exclusion criteria for Module 1 are:

1 Follicular lymphoma grade 3B.

2 Known transformation to aggressive lymphoma, eg, large cell lymphoma.

3 This criterion was removed in Amendment 03; refer to Protocol Amendment Summary of Changes Table for more information.

4 Patients who, in the Investigator's opinion, require immediate cytoreductive therapy for disease control.

13.3 Lifestyle Considerations

There are no additional lifestyle considerations for this Module.

14 STUDY INTERVENTION – MODULE 1

14.1 Study Intervention(s) Administered

All patients will receive treatment with the investigational product capivasertib.

Table 8 Investigational Product

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 will be provided in white high-density polythene bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement.		

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

14.2 Dose Modification

14.2.1 Capivasertib Dose Modification and Guidance

Substantial acute toxicities should be managed as medically indicated and with temporary suspension of capivasertib as appropriate. Recommendations for the management of general

and specific capivasertib-related toxicities are provided in Appendix G of the Core Protocol.

Dose reductions or holds are allowed as clinically indicated by the Study Physician. For each patient, a maximum of 2 dose reductions will be allowed. Guidance on dose level reduction is presented in Table 9.

Table 9 Capivasertib Dose Level Modifications

Dose Level	Capivasertib Oral Daily Dose
Starting Dose	intermittent (4 days on / 3 days off), 480 mg (CCI -mg tablets) BD
-1 Dose Level	intermittent (4 days on / 3 days off), CCI mg (CCI -mg tablets) BD
-2 Dose Levels	intermittent (4 days on / 3 days off), CCI mg (CCI -mg tablets) BD

BD: twice daily.
Dose re-escalations are not allowed.

15 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL – MODULE 1

15.1 Discontinuation of Study Intervention

There are no additional criteria for a patient to be discontinued from capivasertib monotherapy. Refer to the Core Protocol, Section 7.1.

Criteria for stopping or pausing the study recruitment

At any time point during the trial, the study recruitment will pause if at least one of the following events occur:

- Fatal event deemed related to study therapy by the sponsor and in discussion with the SSC (probable or certain causality based on World Health Organisation-Uppsala Monitoring Centre after full aetiological work-up). This will also result in a comprehensive review of safety.
- Unexpected and life-threatening non-hematologic events deemed related to study therapy by the sponsor and in discussion with the SSC. Note: As hyperglycaemia, rash, diarrhoea and hypersensitivity reactions are expected adverse reactions these events will be further addressed at the time of the safety interim analysis described below and will not be considered as stopping criteria.
- Sponsor decision that study participants are placed at undue safety risk.

- Sponsor decision to discontinue the development of the study treatment in the proposed indications.

At the time of interim safety analysis (after approximately 30 patients in Module 1 have had the opportunity to be treated for 8 weeks), the study recruitment may be paused, pending investigation by the sponsor in discussion with SSC, if at least one of the following events occur:

- An increase in the incidence of Grade ≥ 3 Important Identified Risks of hyperglycaemia, diarrhoea, and rash (irrespective of Investigator-determined causality), compared to the reported incidence in solid tumour patients. The proposed limits would correspond to:
  - > 34% participants experiencing Grade ≥ 3 diarrhoea
  - > 40% participants experiencing Grade ≥ 3 hyperglycaemia
  - > 27% participants experiencing Grade ≥ 3 maculo-papular rash
- ≥ 2 patients experiencing systemic drug hypersensitivity reactions
- >22% of participants discontinuing study treatment due to any grade, causally-related AE (ie, > 10% increase compared to the reported incidence is solid tumour patients).
- ≥ 3 patients (≥ 10%) developing a persistent (ie, lasting more than 21 days despite supportive care) Grade ≥ 3 cytopenia (ie, neutropenia, anaemia or thrombocytopenia) within the first 28 days of capivasertib treatment, that in the opinion of the Investigator, cannot be clearly attributable to baseline bone marrow involvement by lymphoma or to extraneous cause.

In the event that the accrual is paused, AZ will notify Investigators, IRB and Regulatory Authorities immediately.

Study recruitment initially paused will restart only upon approval by Regulatory Authorities and IRB/IEC of a substantial protocol amendment, containing additional information on benefit/risk and safety measures as applicable.

For patients who are receiving capivasertib while the decision to stop or pause study accrual is under consideration:

- The Investigator should promptly inform the patients of the possible harm.
- An individual risk/benefit assessment should be conducted by the Investigator and by the sponsor in order to decide whether the risks of continuing the study treatment overweight the benefit, taking into account multiple factors including the disease response to treatment, the number of cycles already received, prior comorbidities and AEs experienced in the trial.

- Overall decision to stop dosing should be taken in conjunction with SSC.

All potential safety signals arising from Grade ≤ 4 treatment-related AEs will be reviewed in the context of the overall benefit-risk. Upon review, any AE deemed to adversely affect the overall benefit risk, will trigger an ad hoc SSC for comprehensive safety review and protocol amendment as needed.

15.2 Temporary Discontinuation

Treatment with capivasertib may be interrupted up to 21 days, for the management of capivasertib-related toxicities and may be restarted, as recommended in Appendix G of the Core Protocol. If treatment cannot be restarted within 21 days (except for rash, within 28 days), it will be permanently discontinued.

16 STUDY ASSESSMENTS AND PROCEDURES – MODULE 1

16.1 Overdose

The maximum tolerated dose for capivasertib and recommended dosing schedule is 480 mg BD 4 days on / 3 days off as monotherapy on intermittent dosing schedule.

17 STATISTICAL CONSIDERATIONS – MODULE 1

17.1 Statistical Hypotheses

Cohorts 1A (FL) and 1B (MZL)

For ORR the following hypothesis will be analysed at the 5% 2-sided level for each of the cohorts.

H0: ORR = 40% versus

H1: ORR = 55%.

Cohort 1C (MCL)

For ORR the following hypothesis will be analysed at the 5% 2-sided level:

H0: ORR = 25% versus

H1: ORR = 40%.

17.2 Sample Size Determination

Cohorts 1A (FL) and 1B (MZL)

CCI [redacted]

CCI [redacted]

Cohort 1C (MCL)

CCI [redacted]

17.3 Statistical Analyses

17.3.1 General Considerations

Table 10 details which data will be analysed at each time point.

Table 10 Summary of analyses and data cut-off triggers

Analysis	Trigger	Data type included
Safety Interim	After approximately 30 patients in Module 1 have had the opportunity to be treated for at least 8 weeks.	Safety data. Preliminary efficacy data based on investigator responses will also be included.
Efficacy Interim	Cohorts 1A and 1B: After 28 patients (either FL or MZL) treated with capivasertib have had the opportunity to be treated for 4 months. Cohort 1C: After 24 patients (MCL) treated with capivasertib have had the opportunity to be treated for 4 months.	Efficacy data (including ORR, DoR, PFS, TTR, and TFST). Safety data will also be included.
Primary Analysis	After all patients treated with capivasertib have had the opportunity to be treated for 6 months. Analyses will be conducted separately for each cohort.	All data (including summary OS data available at the time of the primary analysis).
Final Analysis	Approximately 18 months after the last patient treated with capivasertib has been enrolled in the cohort or when 70% of patients have progressed or died (due to any reason) in the cohort, whichever occurs first. Analyses will be conducted separately for each cohort.	All data (including summary OS data available at the time of the final analysis).

Analysis	Trigger	Data type included
OS Follow-up Analysis	After the final analysis until 70% of patients treated with capivasertib have died due to any cause. Analyses will be conducted separately for each cohort.	OS

DoR: duration of response; FL: follicular lymphoma; MCL: mantle cell lymphoma; MZL: marginal zone lymphoma; ORR: objective response rate; OS: overall survival; PFS: progression-free survival, TFST: Time to first subsequent therapy or death; TTR: Time to objective response.

Additional data cuts may also be performed, if required.

17.4 Interim Analyses

Interim analysis for safety

An interim analysis for safety will be conducted after approximately 30 patients across the three cohorts 1A, 1B, and 1C in Module 1 have had the opportunity to be treated for at least 8 weeks.

A comprehensive review of all available clinical and PK/PD data (if available) will be performed by AZ together with the SSC. Based on these findings should any new safety signals emerge, AZ may opt to amend the protocol to adjust dosing schedule and/or toxicity management guidelines.

This interim analysis will also include preliminary efficacy data using results based on investigator response.

Recruitment will not be paused while the interim analysis is evaluated. The SAP will describe the planned interim analysis in greater detail.

Interim analysis for efficacy

Cohorts 1A (FL) and 1B (MZL)

An interim analysis will be performed after a total of 28 patients enrolled in Cohort 1A plus Cohort 1B have had the opportunity to be treated for 4 months.

The interim analysis will be performed using results from BICR.

This interim analysis will be assessed against a decision framework (Frewer et al 2016) for ORR based on a lower reference value of 40% and a target value (a desired signal to be observed) of 55%. The interim analysis will be based on data from patients from the 2 cohorts combined.

With 28 patients treated with capivasertib monotherapy who have had the opportunity to be treated for 4 months, it may be considered futile to continue development of these cohorts if

there is < 10% probability for the ORR to be greater than 55%. This translates into observing 11 or fewer responders out of 28 patients; an ORR of 40% which has a 2-sided exact binomial 80% CI of 26.7% to 53.2%; wherein the upper confidence limit is below 55%.

Additionally, a greater than 80% probability for the ORR to be above 40% may be considered a good signal. This translates into observing 14 or more responders out of 28 patients; an ORR of 50%, which has a 2-sided exact binomial 60% CI of 40.4% to 59.6% wherein the lower confidence limit is above 40%.

Recruitment will not be paused while the interim analysis is evaluated.

Based on the interim results, study enrolment could pause and the sponsor may opt to amend the protocol to adjust dosing schedule based on emerging data, permanently close the specific cohort or add in a new cohort evaluating capivasertib in combination with other agents in that population which would be detailed in an amendment.

The SAP will describe the planned interim analysis in greater detail.

Cohort 1C (MCL)

An interim analysis will be assessed against a decision framework (Frewer et al 2016) for ORR based on a lower reference value of 25% and a target value (a desired signal to be observed) of 40%.

With 24 patients treated with capivasertib monotherapy who have had the opportunity to be treated for 4 months, it may be considered futile to continue development of this cohort if there is < 10% probability for the ORR to be greater than 40%. This translates into observing 6 or fewer responders out of 24 patients; an ORR of 25% which has a 2-sided exact binomial 80% CI of 13.7% to 39.8%; wherein the upper confidence limit is below 40%.

Additionally, a greater than 80% probability for the ORR to be above 25% may be considered a good signal. This translates into observing 9 or more responders out of 24 patients; an ORR of 38%, which has a 2-sided exact binomial 60% CI of 27.8% to 48.2% wherein the lower confidence limit is above 25%.

Recruitment will not be paused while the interim analysis is evaluated.

Based on the interim results, study enrolment could pause and the sponsor may opt to amend the protocol to adjust the dosing schedule based on emerging data, permanently close the specific cohort or add in a new cohort evaluating capivasertib in combination with other agents in that population which would be detailed in an amendment.

The SAP will describe the planned interim analysis in greater detail.

18 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Patients or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorised representative.

Patients who are rescreened are not required to sign a new ICF if the rescreening occurs within 28 days of the signing of the ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorised designee will explain to each patient the objectives of the analysis to be done on the samples and any potential future use. Patients will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

Potential Changes to Informed Consent During the COVID-19 Outbreak

General Principles

The rights, safety, and wellbeing of the study patients are the most important considerations and should prevail over interests of science and society. All informed consent activities must follow ICH GCP; the CSP; and local laws, regulations, and guidance. Prospective protocol waivers with respect to enrolment remain unacceptable. Patients should not be included in studies without written informed consent according to national laws and regulations and proper eligibility assessment.

The reconsent process described in this appendix must be adopted only at sites/countries affected by the COVID-19 outbreak where reaching the site means placing the study patient under unnecessary risk. The described process does not overrule local laws, regulations and guidance; where differences arise, the latter must be followed.

If the need for re-consenting study patients arises, visiting the investigator sites for the sole purpose of obtaining reconsent should be avoided.

Any validated and secure electronic system already used in the study for obtaining informed consent can be used as per usual practice and if in compliance with local regulations.

Process for Reconsent of Study Patients at Sites Affected by the COVID-19 Outbreak

Before reconsent is obtained, the approved updated patient information sheet and consent form should be provided to study patients by email. If the study patient is not able to receive emails, courier or mail should be used.

Verbal consent via phone or teleconference is allowed.

If possible, verbal consent should be supplemented with email confirmation. The investigator should emphasise that study patients should only use email to confirm their ICF consent and that the patient should not include any sensitive personal identifier (eg, date of birth, social security number) or medical information including AEs.

Please note: Study patients should not sign the document at home after giving verbal consent. The phone call or teleconference should be informative. The document will be signed and filed with the patient's source data once the study patient is able to attend the site. Under no circumstances should the study patient scan and send the document back via email.

Verbal consent and print-out of the email confirmation (if available and once possible) must be documented by the investigator or delegate (if applicable) in the study patient's medical records.

Documentation should include details on when the contact took place, the reason why the

study patient could not reach the site, any important details of the consenting call/concerns raised, and any questions raised (especially on safety measures) by the study patient and that these were answered satisfactorily by the site consenting party.

At the earliest possible occasion, consent must be documented via standard consent process. This would not apply if the study patient is lost to follow-up, dies, or the study ends before the COVID-19 outbreak is over. In this case the reason why the study patient did not sign the document in person has to be documented in the study patient's medical records.

A 4 Data Protection

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the patient in the informed consent.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

The safety of all clinical studies is closely monitored on an on-going basis by the sponsor in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the protocol and letters to investigators.

This study will have an SSC. The primary responsibility of the SSC will be to provide guidance on design, conduct, analysis, and reporting of this trial at the sponsor's request. Decisions and recommendations of the Committee are not binding on the Company. Full details on the SSC are provided in a charter separate from this protocol.

A Safety Review Committee may be established in case a module evaluating capivasertib in combination with other agents is added in the future.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All patient data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the source data agreement for each site.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

Patients from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support

publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study Phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above

Adverse Events for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new

malignant tumour (ie, it is *not* the tumour for which entry into the study is a criterion and that is being treated by the Investigational Product under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B-cell chronic lymphocytic leukaemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumour.

Life-threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself an serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale:

The grading scales found in the revised NCI CTCAE v5 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study treatment that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature

- Wrong patient received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to patient (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures patient's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that patient, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate,

and the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care, and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a saliva sample will be collected for DNA analysis from consenting patients.
- This optional genetic research may consist of the analysis of the structure of the patient's DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

- All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol and in the relevant Module and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of Consent for Genetic Research

- Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main Clinical Study Protocol.

Collection of Samples for Genetic Research

- CCI [redacted] Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE. Only one sample should be collected per patient for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).
- The link between the patient enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

- The genetic component of this study is optional, and the patient may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The PI(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data Management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual patient data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the study treatment.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law
Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law
Aspartate aminotransferase or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the study treatment, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the

elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Local Laboratories Being Used:

The investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention (see Section E 6).
- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For patients that met PHL criteria prior to starting study treatment, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the patient's condition.
- The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
  - Complete the three Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the study treatment, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF

- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the study treatment:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to study treatment and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Intervention

This section is applicable to participants with liver involvement by the disease who meet PHL criteria on study treatment, having previously met PHL criteria at a study visit prior to starting study intervention.

At the first on-study intervention occurrence of PHL criteria being met the investigator will determine if there has been a significant change in the participants' condition# compared with the last visit where PHL criteria were met#

- If there is no significant change no action is required

- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section E 4.2

E 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

> Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver disease or did the participant meet PHL criteria prior to starting study intervention and at their first on-study intervention visit as described in section E 6 of this Appendix?

If **No**: follow the process described in Section E 4.2 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change[#] follow the process described in Section E 4.2 for reporting PHL as an SAE

[#] **A 'significant' change** in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 8 References

Aithal et al 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al Case definition and phenotype standardization in drug-induced liver injury. Clin Pharm Therap 2011;89(6):806-15.

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FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation.

Appendix F Concomitant Medications

F 1 Guidance Regarding Potential Interactions of Capivasertib With Concomitant Medications

Authorized/approved COVID-19 vaccines can be given to patients enrolled in this trial as long as these do not represent a prohibited concomitant medication as detailed in Table F16. Investigators should follow the Clinical Study Protocol, their local prescribing information, and policies when considering if vaccination against COVID-19 is appropriate for their patients participating in an AstraZeneca clinical trial.

The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

POTENTIAL PHARMACOKINETIC INTERACTIONS

Before study treatment

Drugs that should not be combined with capivasertib must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in Table F11 to Table F13.

During study treatment

It is recommended that drugs which should not be combined with capivasertib are not co-administered in accordance with guidance provided in Table F11 to Table F14; however, if it is considered essential for patient management to co-administer these drugs with capivasertib, participants should be monitored closely for possible drug interactions.

Drugs That May Influence Capivasertib Pharmacokinetics

Based on results from *in vitro* studies, capivasertib is primarily metabolised by CYP3A4 and UGT2B7 enzymes. Therefore, inhibitors or inducers of these enzymes may increase or decrease exposure, respectively, to capivasertib.

Co-administration of the strong CYP3A4 inhibitor itraconazole increased capivasertib Cmax by 70% and AUC by 95% (study D3614C00004) and co-administration with the strong CYP450 inducer enzalutamide was estimated to result in approximately 50% reduction in capivasertib AUC and Cmax (RE AKT study; Kolinsky et al 2017).

Strong inhibitors and strong inducers of CYP3A4 must not be combined with capivasertib and must be stopped at least 2 weeks before the first dose of capivasertib (3 weeks for St John's Wort and 4 weeks for enzalutamide). Strong inhibitors must not be used for 2 days following discontinuation of capivasertib. Moderate inhibitors and inducers of CYP3A4 or UGT2B7

inhibitors and inducers are permitted, but caution should be exercised and participants monitored closely for possible drug interactions.

Drugs known to be inhibitors and inducers of CYP3A4 or UGT2B7 are presented in Table F11 and Table F12, respectively. These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate CYP3A4 or UGT2B7 activity.

Table F11 Drugs Known to be Inhibitors of CYP3A4 or UGT2B7

Must be stopped 2 weeks prior to capivasertib administration. Must not be used concomitantly with capivasertib and for 2 days following discontinuation of capivasertib:	**Drugs are permitted but caution should be exercised and participants monitored closely for possible drug interactions:**
Strong CYP3A4 inhibitors boceprevir clarithromycin (+TdP risk) cobicistat danoprevir and ritonavir [a] elvitegravir and ritonavir [a] indinavir and ritonavir [a] itraconazole ketoconazole lopinavir and ritonavir [a] nefazodone nelfinavir paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) [a] posaconazole ritonavir [a] telaprevir telithromycin tipranavir and ritonavir [a] troleandomycin voriconazole	**Moderate CYP3A4 inhibitors aprepitant** ciprofloxacin (+TdP risk) cyclosporine diltiazem erythromycin (+TdP risk) fluconazole (+TdP risk) fluvoxamine tofisopam verapamil
Strong or Moderate CYP3A4 inhibitors AND Sensitive CYP3A substrates Follow Guidance in Table F13: conivaptan dronedarone saquinavir [a]	**UGT2B7 inhibitors** cannabidiol [b]

[a] Ritonavir has dual effects of simultaneous CYP3A inhibition and induction; the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity. Ritonavir is usually given in combination with other protease inhibitors. Please refer to the full Prescribing Information for these drugs prior to co-administration with capivasertib.

[b] Cannabidiol is also a CYP3A4 substrate.
CYP=Cytochrome P450
TdP risk= Known risk of Torsades de Pointes according to the Arizona Centre for Education and Research on Therapeutics (ArizonaCert) website (https://www.crediblemeds.org/). Consider additional ECG monitoring.

Table F12 Drugs Known to be Strong or Moderate Inducers of CYP3A

Must be stopped 2 weeks (3 weeks for St John's Wort) prior to capivasertib administration. Must not be used concomitantly with capivasertib	Drugs are permitted but caution should be exercised and participants monitored closely for possible drug interactions:
Strong CYP3A inducers carbamazepine phenytoin rifampicin/rifampin St. John's wort	**Moderate CYP3A inducers** bosentan efavirenz etravirine phenobarbital primidone

CYP=Cytochrome P450

Drugs That May be Influenced by Capivasertib

There are currently no data confirming that there are any PK interactions between capivasertib and drugs metabolized by CYP450 enzymes. Likewise, there are no confirmed interactions with renal or hepatic transporter substrates. The potential interactions are considered on the basis of preclinical data and physiology-based PK modelling. These suggest that capivasertib may be a moderate to strong inhibitor of CYP3A4, but a less potent inhibitor of some drug transporters and may thus increase the exposure of some drugs. Capivasertib also inhibited CYP2D6 and CYP2C9 in vitro. However, based on physiology-based PK modelling, the increase in exposure of sensitive substrates for these isoenzymes is not predicted to be clinically relevant (<10%).

The guidance below (Table F13 and Table F14) are based on the predicted magnitude of increase in exposure and the expected clinical significance of that increase (therapeutic window and/or QT liability). The lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to be sensitive to inhibition of CYP3A or transporter proteins. Please refer to the full Prescribing Information for all drugs prior to co-administration with study intervention and consider dose reduction where clinically applicable.

Table F13 Drugs Known to be Sensitive or Moderate Sensitive CYP3A Substrates Whose Exposure, Pharmacological Action, and Toxicity May be Increased by Capivasertib

Must be stopped 1 week prior to capivasertib administration. Must not be used concomitantly with capivasertib and for 1 week following discontinuation of capivasertib.	Drugs are permitted but caution should be exercised and participants monitored closely for possible drug interactions.
Sensitive substrates alfentanil avanafil conivaptan dronedarone eletriptan eplerenone ivabradine lomitapide lovastatin lurasidone naloxegol nisoldipine quetiapine saquinavir [a] simvastatin sirolimus tacrolimus ticagrelor tolvaptan triazolam vardenafil	**Sensitive substrates** budesonide buspirone darifenacin darunavira eastine felodipine indinavir [a] maraviroc midazolam sildenafil tipranavir [a]
Moderate sensitive substrates alprazolam atorvastatin eliglustat pimozide (+TdP risk)	**Moderate sensitive substrates** amlodipine aprepitant buprenorphine codeine colchicine fentanyl haloperidol methylprednisolone oxycodone rivaroxaban [b] sertraline tadalafil

[a] Usually administered to patients in combination with ritonavir, a strong CYP3A inhibitor. No clinically significant additional increase in exposure is expected by capivasertib when combined with ritonavir.
[b] Rivaroxaban must not be used concomitantly with both capivasertib and P-gp inhibitors.
CYP=Cytochrome P450

TdP risk= Known risk of Torsades de Pointes according to the Arizona Centre for Education and Research on Therapeutics (ArizonaCert) website (https://www.crediblemeds.org/). Consider additional ECG monitoring.

Table F14 Drugs Known to be Substrates for Renal or Hepatic Transporters Whose Exposure, Pharmacological Action, and Toxicity May be Increased by Capivasertib

Medication	Usage	Rationale
Dofetilide	May be used with caution [a]	MATE1 and OCT2 substrate with a narrow therapeutic window whose exposure may be increased by capivasertib (TdP risk)
Metformin	See Appendix G 2.1	MATE1, MATE-2K and OCT2 substrate whose exposure may be increased by capivasertib
Procainamide	May be used with caution [a]	OCT2 substrate with a narrow therapeutic window whose exposure may be increased by capivasertib (TdP risk)
Pitavastatin Pravastatin Rosuvastatin	May be used with caution [a] The dose may need to be reduced	OATP1B1 substrates whose exposure may be increased by capivasertib

[a] Drugs are permitted, but caution should be exercised, and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with capivasertib.

MATE1: Multidrug And Toxin Extrusion Protein 1; MATE2: Multidrug And Toxin Extrusion Protein 2; OCT2: Organic Cation Transporter 2.
TdP risk=drug with a known risk of Torsades de Pointes according to the Arizona Centre for Education and Research on Therapeutics (ArizonaCert) website (https://www.crediblemeds.org/). Consider additional ECG monitoring.

Additional Resources

For additional inhibitors, inducers, and substrates please refer to:

https://didb.druginteractionsolutions.org/

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

F 2 Restricted, Prohibited, and Permitted Concomitant Medications/Therapies

Restricted, prohibited, and permitted concomitant medications/therapies are described in Table F15, Table F16, and Table F17. Refer also to the dose modification guidelines for management of study treatment -related toxicities in Appendix G.

Table F15 Restricted Medications/Therapies

Medication/class of drug/therapy	Usage (including limits for duration permitted and special situations in which it's allowed)
Corticosteroids	Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.
Some drugs that may interact pharmacokinetically with capivasertib	May be used with caution. For details, see Table F11 to Table F14

CYP: cytochrome P450.

Table F16 Prohibited Medications/Therapies

Prohibited medication/class of drug/therapy	Usage
Any anti-cancer therapy other than those under investigation in this study (except palliative radiotherapy)	Must not be given concomitantly while the patient is on study treatment. No additional investigational or commercial anti-cancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy will be permitted during the active treatment phase.
Herbal and natural remedies that may interfere with interpretation of study results	Must not be given concomitantly unless agreed by the sponsor
Other investigational drugs while on study	Must not be given concomitantly unless agreed by the sponsor
Live attenuated vaccines (eg, Influenza vaccine delivered as nasal spray)	Not permitted Inactivated vaccines or protein/RNA immunogen vaccines are permitted
Some drugs that may interact pharmacokinetically with capivasertib	For details, see Table F11 to Table F14

Table F17 Supportive Medications/Therapies

Supportive medication/class of drug/therapy	Usage
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate adverse event management, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator except for those medications identified as "prohibited," as listed in Table F16.

Supportive medication/class of drug/therapy	Usage
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc]) except for those medications identified as "prohibited," as listed above	Should be used, when necessary, for all patients except for those medications identified as "prohibited," as listed in Table F16
Haematopoietic growth factors (eg, G-CSF, GM-CSF)	Primary or secondary prophylactic use of G-CSFs may be used to treat treatment emergent neutropenia as indicated by the current ASCO guideline and according to investigator's clinical judgement.
Erythropoietin	May be used at the investigator's discretion for the supportive treatment of anaemia
Anti-emetic therapy (including a 5-HT3-antagonist)	Can be given as needed on a prophylactic and treatment basis in compliance with the standards of the centre's local policy
Non-sedating oral antihistamines (eg, cetirizine, fexofenadine, loratadine)	Can be given as needed on a prophylactic and treatment basis in compliance with the standards of the centre's local policy. For symptomatic treatment of rash, as indicated in the toxicity management guideline (Appendix G 2.2)
Anti-diarrhoeal therapy	For symptomatic treatment of diarrhoea, as indicated in the toxicity management guideline (Appendix G 2.4).
Anti-diabetic agents (metformin, insulin)	For symptomatic treatment of hyperglycaemia, as indicated in the toxicity management guideline (Appendix G 2.1).
Required for management of other medical conditions	As required except for those identified as "prohibited," as listed in Table F16

5-HT3: 5-hydroxytryptamine; ASCO: American Society of Clinical Oncology; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte macrophage colony-stimulating factor.

F 3 References

Kolinsky et al 2020
M P Kolinsky MP, Rescigno P, Bianchini D, Zafeiriou Z, Mehra N, Mateo J, et al. A phase I dose-escalation study of enzalutamide in combination with the AKT inhibitor AZD5363 (capivasertib) in patients with metastatic castration-resistant prostate cancer. Ann Oncol 2020;31(5):619-625.

Appendix G Management of Capivasertib-related Toxicity

G 1 Dose Modifications Due to General Capivasertib-related Toxicities

Treatment with capivasertib should be temporarily interrupted for any intolerable AE regardless of grade or for any AEs ≥ Grade 3 that occur despite optimal supportive care, are not attributable to the disease under investigation, or where the investigator considers the AE of concern to be specifically associated with capivasertib. Dose modification guidelines for capivasertib-related toxicities are shown in Table G15 below. Appropriate and optimal treatment of the toxicity is assumed prior to considering dose modifications. The Study Physician may be consulted prior to discontinuation of study treatment due to toxicities. Please see Section G 2 for the management of capivasertib specific toxicities including hyperglycaemia, maculo-papular rash and other skin reactions, and diarrhoea.

Table G15 Dose Modification for General Capivasertib-related Toxicities

NCI CTCAE v5.0 Toxicity Grade	Action
Grade 1 or 2 clinically significant or intolerable	Hold dosing and follow guidance below, depending on outcome
• Resolves to baseline or clinically tolerable within 21 days of onset	• Resume dosing at same dose or 1 reduced dose level as clinically appropriate
• Does not resolve within 21 days of onset	• Discontinue study treatment and observe patient until resolution
Non-life-threatening Grade ≥ 3	Hold dosing and follow guidance below, depending on outcome
• Grade ≥ 3 toxicity for ≤ 21 days and resolves to ≤ Grade 2 or baseline within 21 days of onset	• Resume dosing at same dose or one reduced dose level as clinically appropriate
• Grade ≥ 3 toxicity for > 21 days	• Discontinue study treatment and observe patient until resolution
Life-threatening events	Discontinue study treatment and observe patient until resolution

CTCAE: Common Terminology Criteria for Adverse Events; NCI: National Cancer Institute.

G 2 Dose Modifications Due to Specific Capivasertib-related Toxicities

G 2.1 Hyperglycaemia

These are general recommendations therefore due consideration should be given to baseline values and fasting condition (and time since food if applicable) when interpreting glucose results. In diabetic patients, it may be beneficial to rule out concomitant aetiologies that could be associated with hyperglycaemia (eg, infections, dehydration, vascular events, glucocorticoids).

Patients should be made aware of symptoms of hyperglycaemia (eg, polydipsia and polyuria).

Dose modification guidelines for capivasertib-related hyperglycaemia are shown in Table G16. In addition, for all grades, patients may receive education on lifestyle changes (eg, a diabetic diet) and consider beginning home glucose monitoring (eg, fasting SBGM once daily) at the discretion of the investigator. If glucose home monitoring is instituted, the capivasertib treatment decision should be based on the morning fasting glucose value obtained prior to the dose of capivasertib.

It is recommended that approaches to the management of capivasertib-induced hyperglycaemia include advice from a diabetologist where appropriate (eg, diabetic patients). Metformin is currently the preferred oral antidiabetic recommended for the management of hyperglycaemia occurring in patients participating in studies of capivasertib (see below for further guidance). If a second agent is required, consideration should be given to the intermittent schedule of capivasertib and the pattern of glucose changes (eg, sulphonylureas should be avoided due to their risk of hypoglycaemia secondary to their mechanism of action).

Table G16 Dose Modifications for Capivasertib-related Hyperglycaemia [a]

NCI CTCAE v5 Toxicity Grade	Action
Grade 1 (Abnormal glucose above baseline with no medical intervention)	Maintain same capivasertib dose level
Grade 2 (Change in daily management from baseline for a diabetic; oral antiglycaemic agent initiated; workup for diabetes)	Asymptomatic: • Maintain same capivasertib dose level • Treatment as per local guidelines, consider the use of oral antidiabetic (eg, metformin) on capivasertib dosing days [see further guidance on choice of antidiabetic agents in text above and below the table] Symptomatic: Appropriate clinical management as per local guidelines • Interrupt capivasertib until resolution of symptoms and fasting blood glucose is ≤ 160 mg/dL or ≤ 8.9 mmol/L (treatment can be interrupted up to 21 days) • Restart at same dose level maintaining appropriate antidiabetic treatment (eg, addition of/higher dose of oral metformin) • Consider consult with the diabetologist

NCI CTCAE v5 Toxicity Grade	Action
Grade 3 (Insulin therapy initiated; hospitalisation indicated)	Hold capivasertib up to 21 days, until resolution of symptoms. Consult with diabetologist • If fasting blood glucose decreases to ≤ 160 mg/dL or ≤ 8.9 mmol/L within 21 days and under appropriate antidiabetic treatment, resume capivasertib at 1 lower dose level • If fasting blood glucose does not decrease to ≤ 160 mg/dL or ≤ 8.9 mmol/L within 21 days following appropriate antidiabetic treatment, permanently discontinue capivasertib
Non-life-threatening Grade 4 (Urgent intervention indicated)	Appropriate clinical management of hyperglycaemia per local guidelines. Consider consult with the diabetologist Consider permanent cessation of capivasertib
Life-threatening Grade 4	Discontinue capivasertib and observe patient until resolution

[a] Patients may receive education on lifestyle changes (eg, a diabetic diet) and consider beginning home glucose monitoring (eg, fasting SBGM once daily) at the discretion of the investigator. If glucose home monitoring is instituted, the capivasertib treatment decision should be based on the morning fasting glucose value obtained prior to the dose of capivasertib.

CTCAE: Common Terminology Criteria for Adverse Events; NCI: National Cancer Institute; SBGM: self-blood glucose monitoring.

Use of Metformin

Metformin is currently the preferred oral antidiabetic recommended for the management of hyperglycaemia occurring in patients participating in studies of capivasertib. Investigators should exercise caution in the dosing and management of patients receiving the metformin/capivasertib combination and must be vigilant for signs of renal impairment and metformin toxicity, such as lactic acidosis and hypoglycaemia, namely: lethargy, hypotension, poor urine output, drowsiness, irritation, tachypnoea, sweating, diarrhoea, and vomiting.

Due to the potential interaction of metformin and capivasertib (caused by inhibition of renal transporters [eg, OCT2] involved in the excretion of metformin), when taking both capivasertib and metformin concurrently, patients should attend the study site for monitoring of serum creatinine at least once per week for the first 3 weeks after initiation of metformin, then at the investigator's discretion.

Metformin should only be given on the days when capivasertib is also administered (the half-life of capivasertib is approximately 7 to 15 hours), and should be withdrawn when treatment with capivasertib is withdrawn, unless otherwise clinically indicated.

Consider withholding of metformin on the days patients are due to have imaging with contrast

(in order to reduce the already low risk of lactic acidosis) as per local guidelines.

G 2.2 Maculo-papular Rash

Dose modifications for capivasertib-related maculo-papular rash, which is the most frequent skin toxicity observed in patients treated with capivasertib, are provided in Table G17. However, these management guidelines can be used for other skin toxicities at the discretion of the investigator and/or following consultation with the dermatologist.

Table G17 Dose Modifications for Capivasertib-related Maculo-papular Rash

NCI CTCAE v5 Toxicity Grade	Action
Grade 1 or 2	Continue dosing at current dose and initiate dermatological treatment: • Topical steroid of moderate strength BD • Non-sedating oral antihistamines
Non-life-threatening Grade ≥ 3 or clinically intolerable	Withhold dosing for up to 28 days and initiate dermatological treatment (topical steroid of moderate strength and non-sedating oral antihistamines) with oral steroid for a short course (eg, up to 2 weeks). Consultation with dermatologist is advised
• Improves to Grade ≤ 1 and tolerable within 28 days from onset	• Continue dermatological treatment [a] and restart dosing at same dose
• Improves to Grade 2 and tolerable within 28 days from onset	• Continue dermatological treatment [a] and restart dosing at reduced dose (1 dose level reduction)
• Does not improve to Grade 2 and tolerable within 28 days from onset	• Continue dermatological treatment [a] and discontinue capivasertib
Life-threatening event	Discontinue capivasertib and observe patient until resolution
• **Recurrence of Grade ≥ 3, or Grade 4 (eg, severe bullous, blistering, or exfoliating skin conditions), or any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)**	Discontinue capivasertib and observe patient until resolution

[a] In patients with persistent rash or previous occurrence of Grade 3 consider secondary prophylaxis by continuing topical steroids and/or non-sedating oral antihistamines.

BD: twice daily; BSA: body surface area; CTCAE: Common Terminology Criteria for Adverse Events; IV: intravenous; NCI: National Cancer Institute.

G 2.3 Hypersensitivity

In the case of hypersensitivity reactions, capivasertib should be discontinued and symptomatic/supportive therapy should be initiated (including with antihistamines and/or steroids) as considered appropriate by the investigator/treating physician. Drug rechallenge is not recommended; any subsequent consideration on rechallenge with capivasertib at the same or a lower dose, with its potential for recurrence of such or more severe events should be

carefully considered against the potential benefits to the individual patient from continuation of capivasertib therapy. Further management should follow local guidelines on management of hypersensitivity reactions.

G 2.4 Diarrhoea

Patients should be instructed to promptly contact investigators if they develop diarrhoea. Alternative aetiologies should be ruled out prior to initiating the dose modifications. Investigators are recommended to prescribe anti-diarrhoeal treatment at the first visit so that patients can start treatment at the first sign of diarrhoea, should it occur. Loperamide is the preferred anti-diarrhoea agent for the management of diarrhoea occurring in patients participating in studies of capivasertib. Dose modifications for capivasertib-related diarrhoea are provided in Table G18.

If diarrhoea is reported, additional details regarding this AE will be collected in the eCRF.

Table G18 Dose Modifications for Capivasertib-related Diarrhoea

NCI CTCAE v5 Toxicity Grade	Action
Grade 1	Maintain same capivasertib dose. Anti-diarrhoeal treatment (eg, loperamide) should be initiated at first report of diarrhoea. Maximise the supportive care (eg, dietary modifications, appropriate hydration therapy, and electrolyte supplements as clinically indicated).
Grade 2	Interrupt capivasertib dose (up to 21 days) until recovery to ≤ Grade 1 and resume dosing at same dose level. Anti-diarrhoeal treatment (eg, loperamide) should be initiated at first report of diarrhoea. Maximise the supportive care (eg, dietary modifications, appropriate hydration therapy and electrolyte supplements as clinically indicated). Consider secondary prophylaxis [a]
Non-life-threatening Grade ≥ 3 • Improves to Grade ≤ 1 within 21 days • Does not improve to Grade ≤ 1 after 21 days	Interrupt capivasertib dose (up to 21 days) and institute appropriate anti-diarrhoeal treatment • Resume dosing at same dose or one reduced dose level as clinically appropriate maintaining treatment for toxicity as necessary and/or start secondary prophylaxis [a] • Discontinue drug
Life-threatening Grade 4	Discontinue capivasertib and observe patient until resolution
Recurrence of Grade ≥ 2 or clinically significant or intolerable toxicity despite secondary prophylaxis	Interrupt capivasertib dose (up to 21 days), maintaining appropriate anti-diarrhoeal treatment

NCI CTCAE v5 Toxicity Grade	Action
• Improves to Grade ≤ 1 or becomes clinically tolerable within 21 days	Resume dosing up to 2 reduced dose levels as clinically appropriate maintaining treatment for toxicity as necessary and/or maintaining secondary prophylaxis [a]
• Does not improve to Grade ≤ 1 clinically significant/remains clinically intolerable after 21 days	• Discontinue capivasertib
• Event assessed to be life-threatening	• Discontinue capivasertib and observe patient until resolution

[a] In patients with persistent Grade 1 diarrhoea (eg, loperamide 2 mg, 2 to 4 times daily).
CTCAE: Common Terminology Criteria for Adverse Events; NCI: National Cancer Institute.

G 2.5 Haematological Toxicities

If a patient experiences a clinically significant **and/or unacceptable haematological toxicity** unless clearly attributable to baseline bone marrow involvement by lymphoma or to extraneous cause, dosing in subsequent cycles will be withheld and may subsequently be reduced or discontinued. See the toxicity management guidelines below for recommendations.

To help determine the relatedness of the event to capivasertib versus the underlying condition, consider clinical characteristics such as baseline blood counts, bone marrow involvement by the underlying disease, long-standing toxicities from prior therapies, and any other clinically significant datapoints.

Dose modifications and management of potential haematological toxicities during treatment with capivasertib.

Refer to Table G19 for dose modifications in case of drug-related haematological toxicities. Capivasertib dose level modification options are presented in the relevant Module.

Table G19 Dose Modifications and Management of Potential Haematological Toxicities During Treatment With Capivasertib

NCI CTCAE v5.0 Toxicity Grade	Clinical Supportive Care	Capivasertib Action
Febrile neutropenia / neutropenic infection Grade 3	Consider introducing growth factors (eg, G-CSF), evaluate subject for infection, and begin antibiotic treatment per institutional guidelines.	Withhold capivasertib until fever/infection is resolved, antibiotics are no longer required (except prophylactic antibiotics) and ANC ≥ 1.0×10^9/L or has returned to baseline First episode: Resume capivasertib at next lowest dose level (1 level dose reduction) Second episode: Discontinue treatment

NCI CTCAE v5.0 Toxicity Grade	Clinical Supportive Care	Capivasertib Action
Febrile neutropenia / neutropenic infection Grade 4 (life-threatening)		Withhold capivasertib until fever/infection is resolved, antibiotics are no longer required (except prophylactic antibiotics) and ANC $\geq 1.0 \times 10^9$/L or has returned to baseline Consider re-initiation of capivasertib at reduced dose after discussion with the Study Physician, if overall clinical benefit Second episode: discontinue treatment
Neutrophil count decreased Grade 3 (0.5 to $< 1.0 \times 10^9$ cells/L) without fever or infection	Monitor neutrophil count weekly and consider introducing growth factors (eg, G-CSF). Consider antimicrobial prophylaxis as per institutional guidelines	Withhold capivasertib. • Upon recovery to ANC $\geq 1.0 \times 10^9$ cells (or to baseline), resume capivasertib at next lowest dose level (1 level dose reduction). • Second episode: withhold capivasertib and upon recovery to ANC $\geq 1.0 \times 10^9$ cells (or to baseline), resume capivasertib at next lowest dose level (2 level dose reduction). • Third episode: discontinue treatment.
Neutrophil count decreased Grade 4 ($< 0.5 \times 10^9$ cells/L) without fever or infection	Monitor ANC at least weekly until ANC recover to $> 0.5 \times 10^9$ cells/L and consider introducing growth factors (eg, G-CSF) and antimicrobial prophylaxis as per institutional guidelines	Withhold capivasertib. • Upon recovery to ANC $\geq 1.0 \times 10^9$ cells (or to baseline), resume capivasertib at next lowest dose level (1 level dose reduction). • Second episode: discontinue treatment.
Grade 3 thrombocytopenia ($<50.0 - 25.0 \times 10^9$/L) **without bleeding**	-	Continue capivasertib at same dose level. • First episode lasting > 7 days: reduce 1 level dose • If no recovery to $\geq 50\times 10^9$/L after 7 days of 1 level dose reduction, reduce by a further dose level (2 level dose reduction) If no recovery to $\geq 50\times 10^9$/L after 2 level dose reduction, discontinue treatment
Grade ≥ 3 thrombocytopenia ($<50.0 - 25.0 \times 10^9$/L) **with clinically significant bleeding**	Monitor platelet counts until platelets are $\geq 75.0 \times 10^9$/L or have returned to baseline. Platelet and blood transfusions as clinically indicated.	Withhold capivasertib. At resolution of bleeding and following discussion with Study Physician, if evidence of clinical benefit, may consider re-challenge at 2 dose levels below current dose. Second episode: consider discontinuation capivasertib.

NCI CTCAE v5.0 Toxicity Grade	Clinical Supportive Care	Capivasertib Action
Grade 4 thrombocytopenia without bleeding	Monitor platelet counts within 7 days and then at least weekly thereafter. Platelet transfusion according to local policies	Withhold capivasertib. • If recovery to ≥ 50 × 10^9/L occurs within 7 days: Restart with capivasertib at same dose level • If recovery to ≥ 50 × 10^9/L occurs between 7 to 21 days: resume dosing at 1 level dose level reduction • If no recovery to ≥ 50 × 10^9/L after 21 days: consider discontinuation
Grade 3 anaemia (Hgb <8.0 g/dL; transfusion indicated)	Manage with supportive care, blood transfusion according to local policies	Continue current capivasertib dose.
Grade 4 anaemia (acute and unexpected onset with life-threatening consequences)	Manage with supportive care, blood transfusion according to local policies	Discontinue capivasertib.

ANC: absolute neutrophil count; CTCAE: Common Terminology Criteria for Adverse Events; G-CSF: granulocyte colony stimulating factor; NCI: National Cancer Institute.

Appendix H Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) during which patients may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the patient's safety. If in doubt, please contact the AstraZeneca Study Physician.

H 1 Reconsent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections H 2 to H 6. Local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal consent/reconsent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

H 2 Rescreening of Patients to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened patients. The investigator should confirm this with the designated Study Physician.

In addition, during study disruption there may be a delay between confirming eligibility of a patient and either enrolment into the study or commencing of dosing with study treatment. If this delay is outside the screening window specified in Section 5.4, the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a patient in addition to that detailed in Section 5.4. The procedures detailed in Section 5.4 must be undertaken to confirm eligibility using the same randomisation number as for the patient.

H 3 Home or Remote Visit to Replace On-site Visit (Where Applicable)

A qualified HCP from the study site or TPV service will visit the patients home / or other remote location as per local standard operating procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

H 4 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix, the term telemedicine visit refers to remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow AEs, concomitant medication, and PRO questionnaires to be reported and documented.

H 5 At-home or Remote Location Study Intervention Administration Instructions

If a site visit is not possible, at-home or remote location administration of study treatment may be performed by a qualified HCP, provided this is acceptable within local regulation/guidance, or by the patient or his/her caregiver. The option of at-home or remote location study treatment administration ensures patients safety in cases of a pandemic where patients may be at increased risk by travelling to the study site. This will also minimise interruption of study treatment administration during other study disruptions, eg, site closures due to natural disaster.

H 5.1 At-home or Remote Location Study Intervention Administration by a Qualified HCP or TPV Service (if Applicable)

A qualified HCP from the study site or TPV service should administer the study treatment at the patient's home or other remote location according to the CSP, if applicable. All necessary supplies and instructions for administration and documentation of study treatment administration will be provided. Additional information related to the visit can be obtained via a telemedicine or home visit.

H 5.2 At-home or Remote Location Study Intervention Administration by the Patient or His/Her Caregiver

Prior to at-home or remote location study treatment administration the investigator must assess the patient or his/her caregiver to determine whether they are appropriate for at-home

or remote location administration of study treatment. Once the patient or his/her caregiver is deemed appropriate for at-home or remote location administration, he/she must receive appropriate training. All necessary supplies and instructions for administration and documentation of study treatment administration will be provided. More information related to the visit can be obtained via a telemedicine or home / remote visit.

H 6 Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home / remote visits will be captured by the qualified HCP from the study site or TPV service, or by the patient.

Appendix I Lugano 2014 Classification for Non-Hodgkin Lymphoma

Disease response assessment will be evaluated using the Lugano 2014 Classification for NHL (Cheson et al 2014).

Response assessments will be done by the investigators and independently assessed by the BICR, as determined by Lugano 2014 Classification response criteria. The BICR will conduct response evaluations in accordance with the BICR charter (provided separately from this protocol). Primary and secondary efficacy endpoints will be based on BICR review. Blinded independent central review assessment will not be reported back to Sites. Investigator's assessment overall disease response will also be collected in eCRF.

Tumour assessment will be made for target lesions (ie, measurable disease), non-target lesions (ie, non-measurable disease), organ enlargement (eg, spleen, liver), and new lesions on CT and combined with visual assessment of PET-CT for response assessment (Cheson et al 2014, Table I20).

Visual Interpretation of PET-CT Scans

Variation in FDG uptake in a nodal or extranodal sites indicative for lymphoma will be visually assessed using the Deauville 5-point scale.

Target lesions

Up to a maximum of 6 dominant, measurable lymph nodal or extranodal lesions should be assessed as target lesions and documented at baseline and throughout the study.

A lesion will be considered measurable if:

- For nodal lesions: LDi > 1.5 cm
- For extranodal lesion: LDi > 1 cm

Lesions visible on PET but not on CT/MRI to be assigned as non-target lesions.

Target nodal or extranodal lesions nodes should be selected according to all of the following:

- They should be clearly measurable in at least 2 perpendicular dimensions
- If possible, they should be from disparate regions of the body
- They should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

The perpendicular long and short axis diameters will be measured and recorded in the transverse plane at baseline and follow-up.

For the selected target lymph nodal lesions, the sum of the product of the perpendicular diameters will be calculated with the percentage change from baseline for assessment of response and nadir for assessment of progression.

Non-target lesions:

All other lesions (including nodal, extranodal, and assessable disease) not selected as target lesions, as well as truly non-measurable sites of disease should be followed as nonmeasurable disease (eg, cutaneous, gastrointestinal, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites) and should be factored into the overall response assessment. Non-target lesions will be documented at baseline and throughout the study. Measurement of these lesions is not required to be documented on the eCRFs.

Spleen involvement

Spleen will be considered to be normal if size of its vertical length (cranial-caudal measurement) is ≤ 13 cm. For patients with splenomegaly at baseline, spleen vertical length will be assessed at screening and all subsequent response evaluations.

Liver involvement

Intrahepatic lesions should be considered as target, non-target or new lesion as applicable. For patients with baseline hepatomegaly, the longest diameter of the liver will be assessed at screening and all subsequent response evaluations.

Bone Marrow involvement

Bone marrow involvement by lymphoma documented by aspirate and/or biopsy will be reported on the eCRF as present or absent.

Table I20 Response Assessment Criteria for Non-Hodgkin Lymphoma

Response and Site	PET-CT Based response	CT-Based Response
Complete:	**Complete metabolic response:**	**Complete radiologic response (all of the following):**
Lymph nodes and extralymphatic sites (target lesions)	Score 1, 2, or 3 [a] with or without a residual mass on 5PS [b]	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease (0 × 0 cm)
Nonmeasured lesion (Non-target)	Not applicable	Absent/normal
Organ enlargement	Not applicable	Regress to normal; spleen vertical length is ≤ 13 cm
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Response and Site	PET-CT Based response	CT-Based Response
Partial:	**Partial metabolic response:**	**Partial remission (all of the following):**
Lymph nodes and extralymphatic sites	Score 4 or 5 [b] with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease:	**No metabolic response:**	**Stable disease:**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease:	**Progressive metabolic disease:**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from visually determined nadir and/or	PPD progression:

Response and Site	PET-CT Based response	CT-Based Response
Extranodal lesions	New FDG-avid foci consistent with lymphoma	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of pre-existing nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another aetiology (eg, infection, inflammation). If uncertain regarding aetiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in studies involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy of myeloid growth factors).

[b] PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Adapted from Table 3: Cheson et al 2014.

5PS: Deauville 5-point scale; CT: computed tomography; FDG: fluorodeoxyglucose; GI: gastrointestinal; IHC: immunohistochemistry; LDi: longest transverse diameter of a lesion; MRI: magnetic resonance imaging; PET: positron emission tomography; PPD: cross product of the LDi and perpendicular diameter; SDi: shortest axis perpendicular to the LDi; SPD: sum of the product of the perpendicular diameters for multiple lesions.

Assessment of new lesions

Appearance of any new lesions > 1.5 cm in any axis during or at the end of therapy, even if all other lesions are decreasing should be considered progression. Increased FDG uptake in a previously unaffected site should only be considered progression after confirmation with other modalities (eg, CT, MRI, biopsy).

In patients with no history of pulmonary lymphoma, new nodules identified by CT are benign and should be considered negative for lymphoma. These lesions typically represent infectious or inflammatory lesions; therefore, if FDG positive, should not be considered positive for lymphoma in the absence of confirmatory tests, (eg, histology).

The presence or absence of new lesions will be recorded in the eCRF.

Overall Response Assessment

The efficacy endpoints are based on the overall response assessment, which is combining the radiological response from PET/CT scans, the bone marrow findings (if applicable) and any additional clinical finding, including cytologic or histopathologic findings for each disease response assessment during the study. The possible outcomes for ORR as CR, PR, SD, PD, Unknown. The Investigator-assessed ORR and respective date will be captured on the eCRF.

Appendix J Disease Prognostic Scores

J 1 Follicular Lymphoma Prognostic Scores

Table J21 FLIPI-1 Criteria

Category	Risk Factor
Age	≥ 60 years
Ann Arbor Stage	III-IV
Haemoglobin level	< 12 g/dL
Serum LDH level	> ULN
Number of nodal sites	≥ 5
Risk Group According to FLIPI Chart	**Number of Factors**
Low	0-1
Intermediate	2
High	≥ 3

FLIPI: follicular lymphoma international prognostic index; LDH: lactate dehydrogenase; ULN: upper limit of normal.

Table J22 FLIPI-2 Criteria

Risk Factors	
Age > 60 years	
Raised beta-2-microglobulin	
Haemoglobin < 12 mg/dL	
Longest diameter of largest involved node ≥ 6 cm	
Bone marrow involvement	
Risk Category and Prognosis	
FLIPI-2 Score	**FLIPI-2 Risk Category**
0	Low risk
1-2	Intermediate risk
3-5	High risk

FLIPI: follicular lymphoma international prognostic index.

Table J23 GELF Criteria

Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm
Any nodal or extranodal tumour mass with a diameter of ≥ 7 cm
B symptoms
Splenomegaly
Pleural effusions or peritoneal ascites
Cytopaenias (leukocytes < 1.0×10^9/L and/or platelets < 100×10^9/L)
Leukaemia (< 5.0×10^9/L malignant cells)

GELF: Groupe d'Etude des Lymphomes Folliculaires.

J 2 Mantle Cell Lymphoma Prognostic Score

Table J24 Simplified MIPI

Point	Age (years)	ECOG	LDH ULN	WBC (10^9/L)
0	< 50	0-1	< 0.67	< 6.700
1	50-59	-	0.67-0.99	6.700-9.999
2	60-69	2-4	1.000-1.49	1.000-14.999
3	≥ 70	-	≥ 1.5000	≥ 15000

For each prognostic factor, 0 to 3 points were given to each patient and points were summed up to a maximum of 11. ECOG performance status was weighted with 2 points if patients were unable to work or were bedridden (ECOG 2-4). LDH was weighted according to the ratio of the ULN. Thus for an ULN of 240 U/L, the cutpoints were 180 U/L, 240 U/L, and 360 U/L, for example.
- indicates not applicable.
ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; MIPI: Mantle Cell Lymphoma International Prognostic Index; ULN: upper limit of normal; WBC: white blood cell.

Table J25 Risk Category According to the MIPI

MIPI Score	Risk
0-3	low
4-5	intermediate
6-11	high

MIPI: Simplified Mantle Cell Lymphoma International Prognostic Index.

J 3 References

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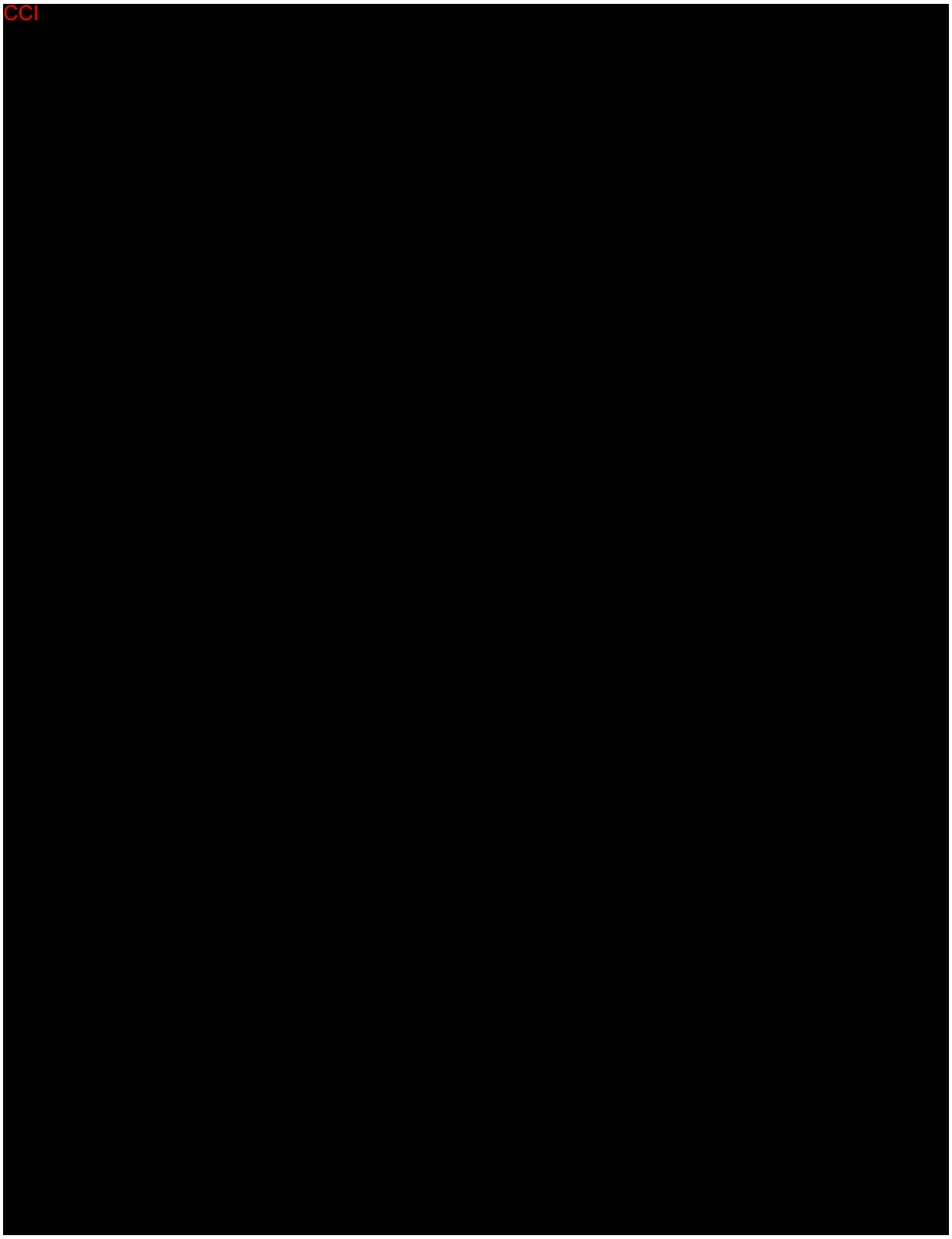
Appendix K Patient-reported Outcomes

K 1 EORTC QLQ-C30

CCI



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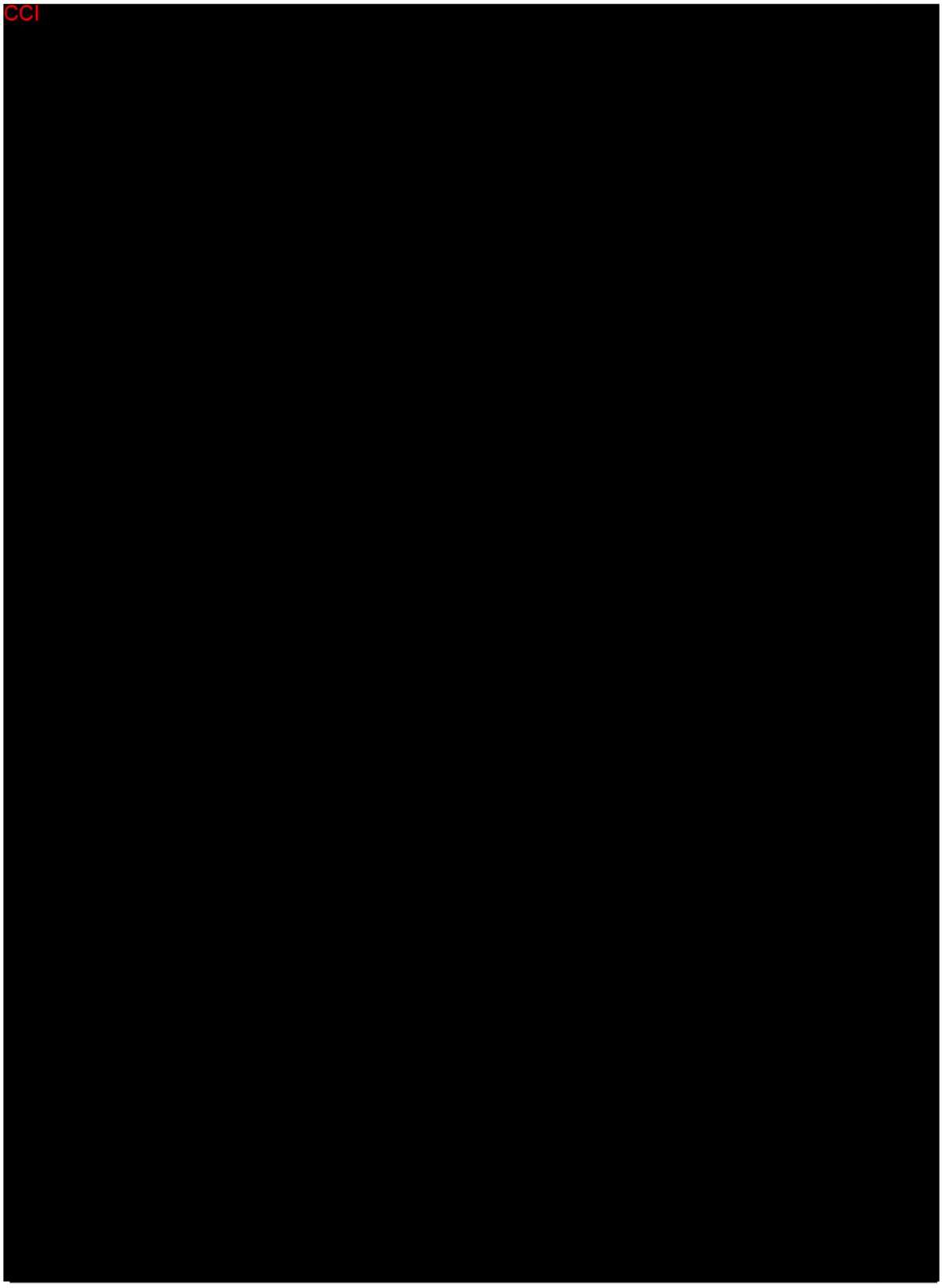

K 2 CCI

CCI

K 3 NCI PRO-CTCAE

NCI PRO-CTCAE ™ ITEMS

Item Library Version 1.0

English

Form Created on 25 January 2021

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days...

1a. In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

2a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
2b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

3a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
3b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

4a. In the last 7 days, how OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
4b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

5a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

6a. In the last 7 days, did you have any RASH?	
O Yes	O No

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7a. In the last 7 days, what was the SEVERITY of your DRY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

8a. In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

9a. In the last 7 days, what was the SEVERITY of your BLURRY VISION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
9b. In the last 7 days, how much did BLURRY VISION INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

10a. In the last 7 days, how OFTEN did you have a HEADACHE?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
10b. In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
10c. In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

11a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
11b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

12a. In the last 7 days, were there times when you had to URINATE FREQUENTLY?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
12b. In the last 7 days, how much did FREQUENT URINATION INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

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K 4 Patient-reported Anti-diarrhoeal Medication

K 5 PGI-TT

CCI

K 6 CCI

CCI

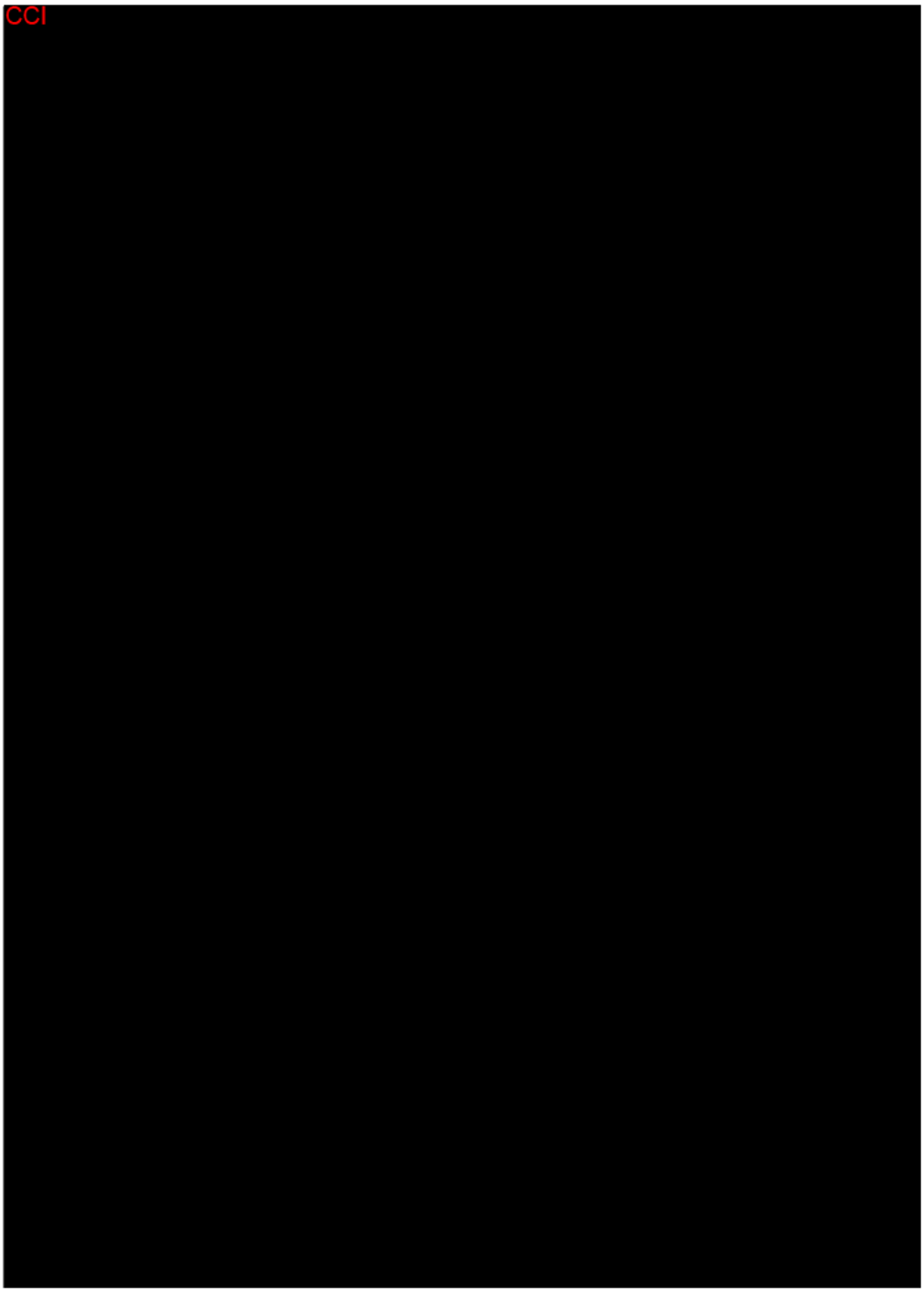
SAMPLE

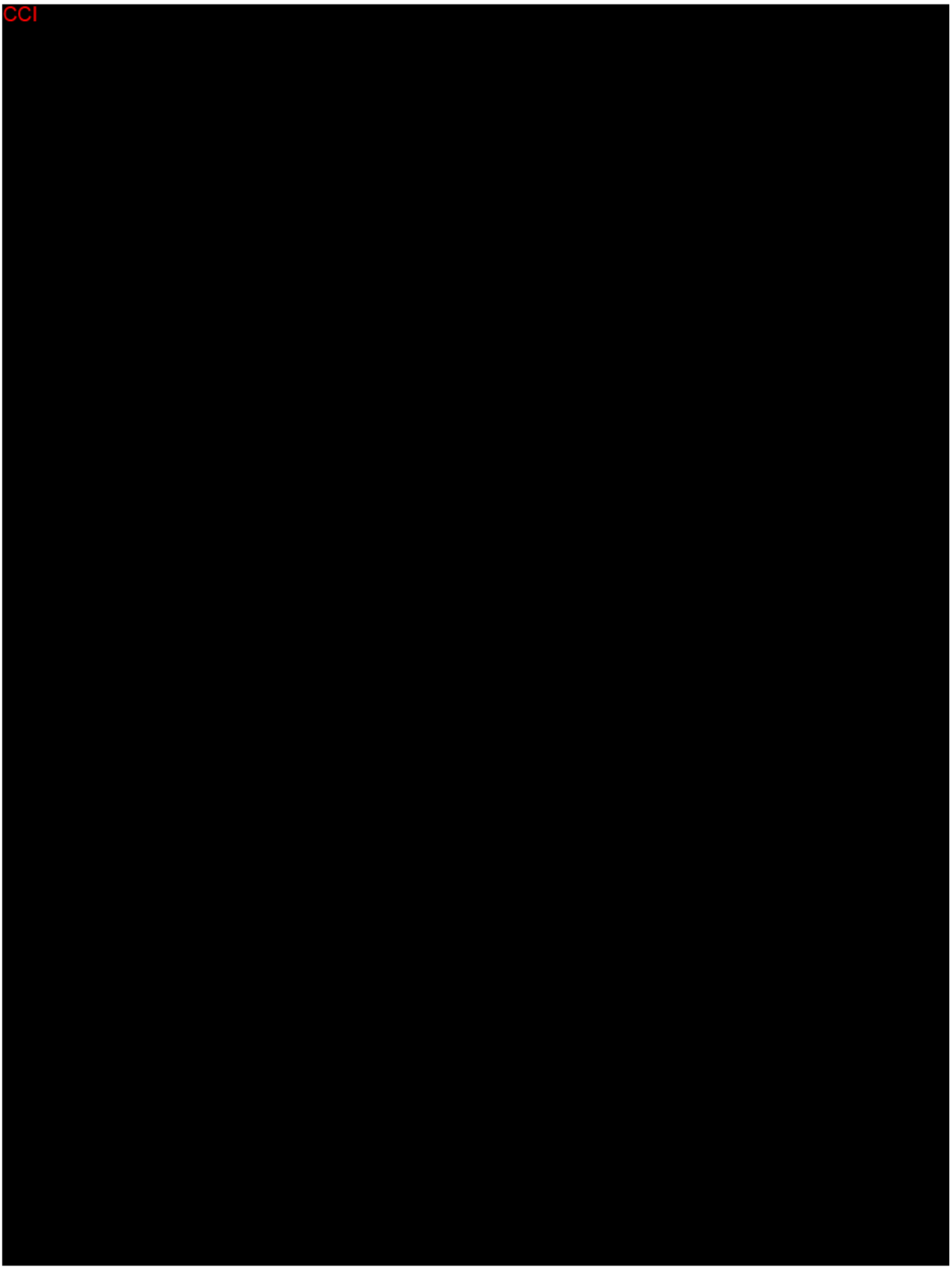
K 7 CCI

CCI

K 8 CCI

CCI

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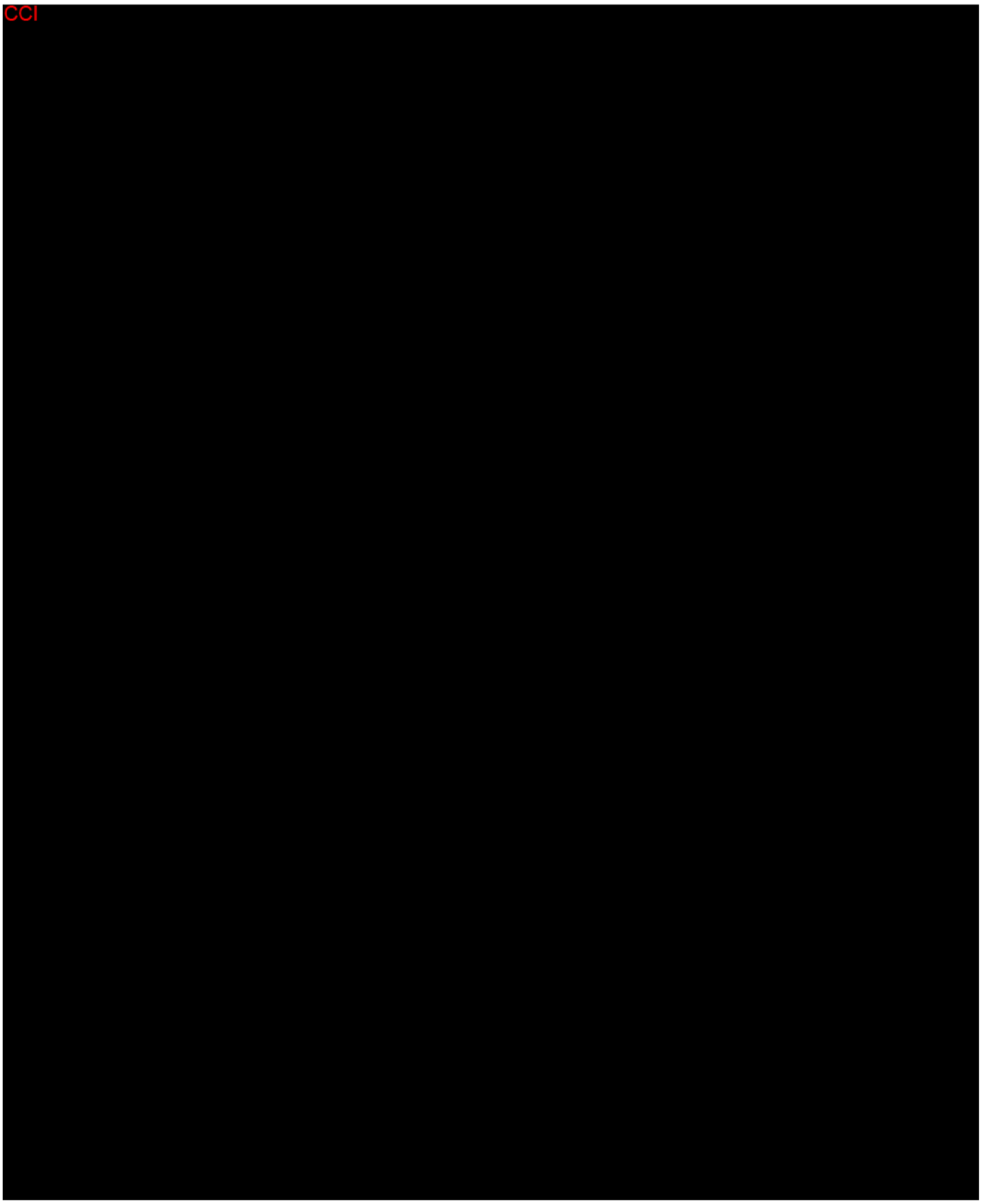
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Appendix L Abbreviations

Abbreviation or special term	Explanation
5-HT3	5-hydroxytryptamine
5PS	Deauville 5-point scale
AE	Adverse event
AESI	Adverse event of special interest
AKT	Activation of Protein Kinase B
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/transaminase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase/transaminase
AUC	Area under plasma concentration-time curve
AUCss	Area under plasma concentration-time curve at steady state
B	Blood
BD	Twice daily
BICR	Blinded independent central review
BSA	Body surface area
BTK	Bruton's tyrosine kinase
BUN	Blood urea nitrogen
C	Cycle
CAR-T	Chimeric antigen receptor T
CD	Cluster of differentiation
CFR	Code of Federal Regulations
cHL	Classic Hodgkin lymphoma
CI	Confidence interval
CL	Central laboratory collection
CMV	Cytomegalovirus
CNS	Central nervous system
COA	Clinical outcome assessment
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	Case report form
CRO	Contract Research Organisation
CSP	Clinical Study Protocol

Abbreviation or special term	Explanation
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	CCI
Ctrough	Observed lowest drug concentration reached before the next dose is administered
CYP	Cytochrome P450
d/D	Day
DBP	Diastolic blood pressure
DCO	Data cut-off
DILI	Drug Induced Liver Injury
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
CCI	CCI
EDC	Electronic data capture
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	End of treatment
ePRO	Electronic patient-reported outcome
CCI	CCI
CCI	CCI
EZH	Enhancer of zeste homolog
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin-fixed paraffin embedded
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GELF	Groupe d'Etude des Lymphomes Folliculaires
GM-CSF	Granulocyte macrophage colony-stimulating factor

Abbreviation or special term	Explanation
HbA1c	Glycosylated haemoglobin A1c
HBc	Hepatitis B core
HBV	Hepatitis B virus
HCP	Health Care Professional
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HL	Hy's Law
HSCT	Haematopoietic stem cell transplant
IATA	International Airline Transportation Associations
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
LDH	Lactate dehydrogenase
LDi	Longest transverse diameter of a lesion
LL	Local laboratory collection
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MATE1	Multidrug And Toxin Extrusion Protein 1
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
MHRA	Medicines and Healthcare Products Regulatory Agency
MIPI	Mantle Cell Lymphoma International Prognostic Index
CCI	CCI
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
MUGA	Multiple-gated acquisition

Abbreviation or special term	Explanation
MZL	Marginal zone lymphoma
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NIMP	Non-investigational medicinal product
NK	Natural killer
NKT	Natural killer T
NYHA	New York Heart Association
OAE	Other significant adverse event
OCT2	Organic Cation Transporter 2
ORR	Objective response rate
OS	Overall survival
P	Plasma
PCR	Polymerase chain reaction
PD	Progression of disease
PET	Positron emission tomography
PFS	Progression-free survival
CCI	CCI
CCI	CCI
PGI-TT	Patient Global Impression of Treatment Tolerability
PHL	Potential Hy's Law
PI	Principal investigator
PI3K	Phosphatidylinositol 3-kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PK	Pharmacokinetic(s)
PPD	Cross product of the LDi and perpendicular diameter
PR	Partial response
PRO	Patient-reported outcome
PRO-CTCAE	Patient-reported Outcomes-Common Terminology Criteria for Adverse Events
PT	Preferred term
PTEN	Phosphatase and tensin homologue
QoL	Quality of life
QTc	Corrected QT interval
QTcF	QT Interval corrected using Fridericia's formula
R/R	Relapsed or refractory
RECIL	Response Evaluation Criteria in Lymphoma

Abbreviation or special term	Explanation
RNA	Ribonucleic acid
RTSM	Randomisation and Trial Supply Management
S	Serum
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SBGM	Self-blood glucose monitoring
SBP	Systolic blood pressure
SD	Stable disease
SDi	Shortest axis perpendicular to the LDi
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SOC	System organ class
SPD	Sum of the product of the perpendicular diameters for multiple lesions
SSC	Study Steering Committee
T4	Thyroxine
TBL	Total bilirubin
TFST	Time to first subsequent therapy or death
TOR	Target of rapamycin
TP53	Tumour protein 53
TPV	Third-party vendor
TSH	Thyroid-stimulating hormone
TTR	Time to objective response
U	Urine
ULN	Upper limit of normal
US	United States
USPI	United States prescribing information
VAS	Visual analogue scale
VTE	Venous thromboembolism
WBC	White blood cell
WOCBP	Woman of child bearing potential

Appendix M Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 02, v3.0 (28 July 2021)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This protocol amendment incorporates changes requested by the French National Agency for the Safety of Medicines and Health Products (ANSM) arising from review of version 2.0 of the protocol, dated 28 April 2021.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 13.1.1 (Additional Inclusion Criteria for Cohort 1A); Section 13.1.3 (Additional Inclusion Criteria for Cohort 1C)	Updated to clarify physicians should discuss CAR-T cell therapy for R/R FL and MCL patients prior to study enrolment	Updated in line with ANSM request	Non-substantial

Amendment 01, v2.0 (28 April 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This protocol amendment incorporates changes requested by the United States Food and Drug Administration (FDA) arising from review of version 1.0 of the protocol, dated 18 February 2021.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 (Synopsis)	Updated to clarify the DCO date for final analysis of each cohort.	Updated in line with FDA request	Non-substantial
Section 5.2 (Core Exclusion Criteria)	• Amended to exclude patients with increased risk of VTE not willing to receive VTE prophylaxis. • Amended to exclude the concomitant use of UGT2B7 inhibitors/inducers.	Amended in response to FDA request	Substantial
Section 5.3.1 (Meals and Dietary Restrictions)	Additional information added on dietary restrictions with capivasertib.	Updated in line with FDA request	Substantial
Section 8.1.2 (Imaging Assessments) and Section 10.1 (SoA, Module 1)	Updated to clarify the use of PET and CT in disease response assessment for MZL patients with and without FDG uptake on baseline.	Updated in line with FDA request	Non-substantial
Section 8.2.2 (Vital Signs) and Section 10.1 (SoA, Module 1)	Updated to align the patient posture requirement (sitting) and resting time (5 minutes) preceding the vital signs assessments	Amended to align the text between 2 sections for consistency	Non-substantial
Section 8.2.3 (ECG) and Section 10.1 (SoA, Module 1)	Updated to align the patient posture requirement (supine) and triplicate ECG time interval (1 minute) during ECG assessments	Amended to align the text between 2 sections for consistency	Non-substantial
Section 9.6 and Appendix A5 (Data Monitoring Committee)	Amended to clarify the frequency of safety data review by the Study Steering Committee	Amended in response to FDA request	Non-substantial
Section 9.4.5 Exploratory Analyses	CCI [redacted]	Updated in line with FDA request	Substantial
Section 12 Figure 1 (Study Design – Module 1)	Amended to include details of planned interim analysis for safety and preliminary efficacy.	Amended in response to FDA request	Substantial
Section 12.1	Updated to include further details on the selection of the dose for capivasertib monotherapy and to provide the rationale for the proposed intermittent dosing schedule	Updated in line with FDA request	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
(12.1 Justification for Dose – Module 1)			
Section 12.2 (End of Study Definition)	Updated to clarify the DCO date for the final analysis of each cohort.	Updated in line with FDA request	Non-substantial
Section 13.1.1 (Additional Inclusion Criteria for Cohort 1A)	Updated to include the current need for systemic treatment and to clarify that all patients with FL must have relapsed, progressed, or be refractory after at least 2 prior lines of systemic therapy	Updated in line with FDA request	Substantial
Section 13.1.2 (Additional Inclusion Criteria for Cohort 1B)	Updated to include the current need for systemic treatment and to clarify that patients with MZL must have relapsed, progressed, or be refractory after at least 2 prior lines of systemic therapy instead of 1	Updated in line with FDA request	Substantial
Section 13.1.3 (Additional Inclusion Criteria for Cohort 1C)	Updated to clarify that patients with MCL must have relapsed, progressed, or be refractory after at least 2 prior lines of systemic therapy instead of 1	Updated in line with FDA request	Substantial
Section 13.2 (Exclusion Criteria)	Amended to clarify that patients with an immediate need for cytoreductive treatment are excluded.	Amended in response to FDA request	Substantial
Section 15.1 (Discontinuation of study intervention and Stopping Criteria)	Amended to include criteria that would stop or pause study recruitment	Amended in response to FDA request	Substantial
Section 17.3 Statistical Analyses	Table 10 amended to include details of interim analyses for safety and clarify the DCO date for the final analysis of each cohort.	Amended in response to FDA request	Substantial
Section 17.4 Interim Analyses	Amended to include interim analysis for safety.	Amended in response to FDA request	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix G (General Capivasertib-Related Toxicities) G 1, G 2.1, G 2.2, G 2.4	Table G15-Table G18 updated to include guidance on treatment dosing in patients who experience life-threatening events	Updated in line with FDA request	Substantial
Appendix G 2.5 Haematological Toxicities	Table G19 updated to include treatment dosing in patients with severe cytopenia. Typographical errors corrected.	Updated in line with FDA request	Substantial
Appendix F Guidance Regarding Potential Interactions of Capivasertib with Concomitant Medications	Amended to include UGT2B7 inhibitors and inducers as drugs that may influence pharmacokinetics. Table F11 updated to include restrictions in the use of cannabidiol Table F13 updated to include details on concomitant use with statins.	Amended in response to FDA request	Substantial

Abbreviations: CT: computed tomography; DCO: data cut-off; ECG: electrocardiogram; FL: follicular lymphoma; IA: interim analysis; FDA: Food and Drug Administration; FDG: Fluorodeoxyglucose; MCL: mantle cell lymphoma; MZL: marginal zone lymphoma; PET: positron emission tomography; R/R: relapsed or refractory; SoA: schedule of assessments; VTE: venous thromboembolism.

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