Parexel International

AstraZeneca

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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)

Statistical Analysis Plan

Version: 3.0

Parexel Project Number: 256606

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	01-Feb-22	New document.
2.0	07-Jul-22	• Updated to be aligned with CSP v6.0. • Updated Section 1 (Introduction). • Section 4.7 minor updates for MCL Cohort 1C . • Section 4.9 summary for prior regimens replaced with summary of prior lines. • Concordance between BICR and investigator´s assessment added (4.11.2). • Summary of censoring rules for PFS added (4.11.3.2). • Duration on study section added (4.12.2) . • Updated Adverse event section (4.12.3, Adverse Events of Special Interest), to be in line with current list of AESIs for capivasertib. Removal of urinary tract infection, pneumonia and Torsades de pointes from the AESI list; addition of infective pneumonia. One characteristic of diarrhoea AEs removed from summaries and the other was updated. • Overdose section added (4.12.4) • Deletion of T/B/NK from “Table 5 Laboratory Safety Variables”. T/B/NK cell count are not part of clinical safety laboratory assessment. Addition of gammaglutamyl transferase to “Table 5 Laboratory Safety Variables”. • Appendices section included. Time windows for Module 1 added.
3.0	19-May-23	SAP updated to follow “Early Onc SAP Template lymphoma_v1.0 2022-12”. Section 4.5 • ECOG [0-1 vs 2] category was removed. Section 4.11.2 • Sum of the product of the perpendicular diameters is collected in cm^2 and will be reported in cm^2 . Section 4.7

		• Prior bispecific TCEs added.
	22-Sep-23	Section 4.11.4 updated to include description for PK analysis.
	13-Nov-23	Identified any analyses not to be conducted or presented due to early termination of the study. Section 3.2.1 updated to include that interim analyses will not be performed due to early termination of the study. Section 4.2 updated to include details about summaries presentation. Section 4.3.2 updated to add further clarification. Section 4.6 Updated information to be included in Disposition of Patient summaries and added in information for the analysis sets summaries. Section 4.6.1 updated to remove 'site' from description of summaries by country and site. Section 4.7 removed patient recruitment as this is mentioned in Section 4.6.1. Section 4.11.1.7 Prior bispecific TCEs added. Section 4.11.2 added further details and clarification for BoR and Tumour assessments. Included Overall disease response into Tumour assessment details. Section 4.11.3 added further details, formulas, and clarification for DoR, PFS, OS, TFST and TTR. Section 4.12.1 Included "+1" in the formula for duration of an interruption. Definitions added for Planned total dose and Actual total dose.

		Section 4.12.3 “total number of diarrhoea events patients experience” removed. Included “+1” in the formulas for time to onset and duration of AESI. Section 4.12.6 Minor updates made to Table 5 Laboratory Safety Variables. Section 4.12.8 RR typo corrected to PR.

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
AESIs	Adverse events of special interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical therapeutic chemical
BICR	Blinded Independent Central Review
BID	Bis in die (twice daily)
BMI	Body Mass Index
BoR	Best objective response
BP	Blood pressure
Bpm	Beats per minute
BTK	Bruton's tyrosine kinase
CART	Chimeric antigen receptor T
CR	Complete response
CI	Confidence interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CCI	CCI
DBP	Diastolic blood pressure
DCO	Data cut off
d/D	Day
DoR	Duration or response
DRM	Data Review Meeting
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
CCI	CCI

Abbreviation / Acronym	Definition / Expansion
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire Core 30
EOT	End of treatment
CCI	CCI
CCI	CCI
eCRF	Electronic Case Resport Form
EOS	End-of-study
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GELF	Groupe d'Etude des Lymphomes Folliculaires
HbA1c	Glycosylated haemoglobin
HR	Heart rate
HSCT	Haematopoietic stem cell transplant
ICH	Immuno-histochemistry
ICF	Informed consent form
Ig	Immunoglobulin
IP	Investigational Medicinal Product
LLOQ	Lower limit of quantification
LTFU	Long-term follow-up
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
CCI	CCI
MTD	Maximum tolerated dose
MUGA	Multiple-gated acquisition
MZL	Marginal zone lymphoma
NA	Not available
NCS	Not clinically significant
NHL	Non Hodgkin lymphoma

Abbreviation / Acronym	Definition / Expansion
ORR	Objective Response Rate
PD	Progression of disease
PI3K	Phosphatidylinositol 3-kinase
PFS	Progression-free survival
CCI	CCI
CCI	CCI
PGI-TT	Patient Global Impression of Treatment Tolerability
PK	Pharmacokinetic
PR	Partial response
PRO	Patient-reported Outcomes
PRO-CTCAE	National Cancer Institute patient-reported outcomes Common Terminology Criteria for Adverse Events
R/R	Relapsed or refractory
QT	The QT interval is measured from the beginning of the QRS complex to the end of the T wave
QTc	Corrected QT interval
QTcF	QT corrected using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System Organ Class
TEAE	Treatment emergent adverse event
ULOQ	Upper limit of quantification
WOCBP	Woman of childbearing potential
WHO-DD	World Health Organization - Drug Dictionary

1 INTRODUCTION

This is a modular, Phase II, open-label, multicentre study of capivasertib in patients with relapsed or refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL).
The statistical analysis plan (SAP) provides a technical elaboration of the statistical analysis to be performed as outlined in the clinical study protocol (CSP). All analyses described in this SAP are applicable for all modules and cohorts unless otherwise stated. Details provided in this document will also support the statistical analysis for conferences and publications.

The analyses described in this SAP are based upon the following study document:

- Study Protocol, Version 6.0 (February 24, 2022)

The specifications for tables, listings and figures are contained in a separate document.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Core

2.1.1 Primary Objective

Objectives	Estimand description
• 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

Objectives	Estimand description
	Lugano 2014 Classification for NHL assessed by the Investigator.

BICR: blinded independent central review; CR: complete response; NHL: non-Hodgkin lymphoma; ORR: objective response rate; PR: partial response.

2.1.2 Secondary Objectives

Objectives	Estimand description
• 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.

Objectives	Estimand description
• 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. 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.

Objectives	Estimand description
	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). 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; CTCAE: Common Terminology Criteria for Adverse Events; Ctrough: observed lowest drug concentration reached before the next dose is administered; PK: pharmacokinetics; 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; PFS: progression-free survival; PGI-TT: Patient Global Impression of Treatment Tolerability; PRO-CTCAE: Patient-reported Outcomes-Common Terminology Criteria for Adverse Events; TFST: time to first subsequent therapy or death; TTR: time to objective response.

2.1.3 Exploratory Objectives

Objectives	Estimand description
• CCI	CCI
• CCI	CCI
• CCI	CCI
• CCI	CCI CCI CCI
• CCI	CCI CCI CCI
• CCI	CCI CCI CCI

Objectives	Estimand description
• CCI	CCI

CCI

Exploratory endpoints will be reported outside of the CSR and will therefore not be described further within this SAP.

2.2 Module 1

Refer to Section 2.1 of the SAP.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Core Module

This is a modular, open-label, multicentre Phase II study of capivasertib administered orally in patients with R/R B-cell NHL.

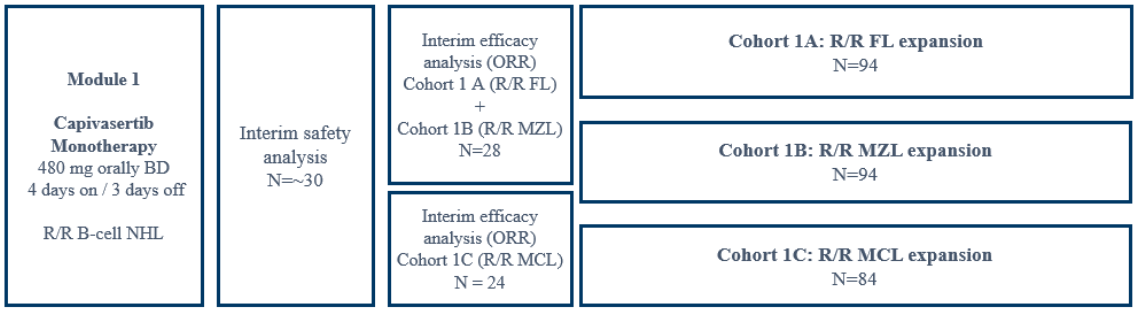
The core module provides the overall framework for the study and specific details are described separately for each module. A substantial protocol amendment with relevant supportive rationale will be approved before starting a new module.

3.1.2 Module 1

Module 1 is investigating capivasertib (AZD5363) monotherapy, administered orally in an intermittent twice daily (BD) (4 days on/3 days off) regimen to patients with R/R FL, R/R MZL, R/R MCL.

The 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.

Module 1 for capivasertib monotherapy will include:

- A Screening Period of up to 28 days
- A Treatment Period comprised of 28-day treatment cycles, during which patients will receive 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 long-term follow-up 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. Survival will be assessed every 12 weeks (± 7 days) and response assessments for patient who stop study treatment without PD.

3.2 Planned Analyses

3.2.1 Module 1

Table 1 Summary of analyses and data cut-off triggers1 details the analyses planned during the conduct of Module 1 and the data cut-off triggers.

Table 1 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.

Analysis	Trigger	Data type 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).
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.

The interim safety and efficacy analyses will not be performed due to early termination of the study (number of patients required for analyses not met).

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

Summaries and analyses will be presented either by cohort and overall, or by cohort alone. Details for each output display are described in TFL-Shells document.

The following considerations will be applicable to all modules.

Continuous data will be summarised using descriptive statistics (number of observations, mean, standard deviation [SD], median, 25^{th} and 75^{th} percentiles [where appropriate], minimum and maximum). Geometric mean and coefficient of variation (CV) may be presented as applicable.

If data are available for less than 3 patients, no summary statistics other than minimum, maximum and number of observations will be presented.

For continuous data, the mean, median and geometric mean will be rounded to one additional decimal place compared to the original data. The SD and CV will be rounded to two additional decimal places compared to the original data. Minimum and maximum will be displayed with same accuracy as the original data. The maximum number of decimal places reported will be four for any summary statistic.

Categorical data will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated from the population total within that cohort. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts.

Time to event variables will be presented using the Kaplan-Meier methodology where appropriate, including median time calculated from the Kaplan-Meier curves.

Confidence intervals (CIs) and p-values, when presented, will generally be constructed at the 2-sided alpha level specified for each module. For Module 1, a 2-sided 95% CIs will be constructed and presented to one additional decimal place compared to the original data.

In general, baseline will be the last non missing value obtained prior to the first dose of study medication and any information taken after first dose of study medication will be regarded as post

baseline information. If two visits are equally eligible to assess participant status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose with no washout or other intervention in the screening period), the average is taken as the baseline value. For non-numeric laboratory tests (i.e. some of the urinalysis parameters) where taking an average is not possible then the best value will be taken as baseline as this is the most conservative. In the scenario where there are two assessments on Day 1 prior to first dose, one with time recorded and the other without time recorded, the one with time recorded is selected as baseline. Where safety data are summarised over time, study day will be calculated in relation to date of first treatment. If no value exists before the first dose/administration, then the baseline value will be treated as missing.

In all summaries:

Change from baseline = post-baseline value - baseline value.

Percent change from baseline =

$$\frac{\text{post-baseline value - baseline value}}{\text{baseline value}} \times 100.$$

4.3 General Variables

4.3.1 Study Day Definitions

Study day 1 is defined as the date of first dose of study treatment (Cycle 1 Day 1).

For visits (or events) that occur on or after first dose of study treatment, study day is defined as (date of visit [event] – date of first dose of study treatment + 1). For visits (or events) that occur prior to first dose, study day is defined as (date of visit [event] – date of first dose of study treatment). There is no study day 0 defined for this study.

4.3.2 Time Windows

For safety and tumour assessments, time windows will be defined for any presentations that summarise values by visit. The following conventions will apply:
For tumour assessments:

- The protocol assigned windows for tumour assessments will be used to assign the result to a particular visit.
- For safety assessments: The time windows will be exhaustive so that data recorded at any timepoint has the potential to be summarised. Inclusion within the time window will be based on the actual date and not the intended date of the visit.
- All unscheduled visit data will have the potential to be included in the summaries.

- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls halfway between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day. Refer to Appendix A for visit windows examples.
- Windowing will be done separately for each assessment based on the schedule of events specific to that assessment.
- Should study day be missing (due to partial or missing dates), then the visit will be assigned to the nominal visit at which the assessment was recorded, and no windowing will be performed.
- Visit windowing will be conducted up and including the EOT visit. That is the EOT visit will be reassigned to a scheduled visit based on the study day the EOT visit occurred at. Follow-up visits will not be windowed.
- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).
- Listings will display all values contributing to a timepoint for a patient.

- For visit-based summaries: If there is more than one value per patient within a time window then the closest value to the scheduled visit date will be summarised, or the earlier, in the event the values are equidistant from the nominal visit. The listings will highlight the value for the patient that contributed to the summary table, wherever feasible. In summaries of extreme values all post-baseline values collected are used including those collected at unscheduled visits regardless of whether the value is closest to the scheduled visit date, or not. For summaries at the patient level, all values will be included, regardless of whether they appear in a corresponding visit-based summary.

4.3.3 Handling of Missing Data

In general, other than for the below described, or where otherwise specified in the particular analysis, missing data will not be imputed and will be treated as missing.

4.3.3.1 Imputations of Partial Dates

Concomitant medication and adverse events start dates

- Missing day: impute with the 1st of the month, unless month and year are the same as month and year of first dose of study treatment, then impute with first dose date.
- Missing day and month: impute with the 1st of January unless the year is the same as the year of first dose of study treatment, then impute with first dose date.
- Completely missing: impute with date of first dose of study treatment, unless the end date suggests it could have started prior to this in which case impute with 1st January of the same year as the end date.

When imputing a start date care should be taken to ensure the start date is sensible, i.e., prior to the end date.

Concomitant medication and adverse events end dates

- Missing day: impute the last day of the month unless both the month and the year are the same as the last dose date or the primary analysis data cut-off (DCO) date then impute the last dose date or the primary analysis DCO date.
- Missing day and month: Impute 31st December unless the year is the same as the last dose date or the primary analysis DCO date then impute the last date or the primary analysis DCO date.
- Completely missing: before imputing a date, consider whether the AE/medication is still ongoing and also when it started in relation to study drug. If the ongoing flag is missing then assume that AE is still present/ medication is still being taken (i.e., do not impute a date). If the AE/medication has stopped and start date is prior to first dose date, then impute first dose date. Or if it started on or after first dose date then impute a date that is after the last dose of study drug date.

Generally, the imputation of dates is used to decide if an observation is treatment emergent for AEs or concomitant for medications. Flags will be retained in the database indicating where any programmatic imputation has been applied, and in such cases, durations and study days will not be calculated.

4.3.4 Imputation Rules for Laboratory Values Outside of Quantification Range

Values of the form "< x" (i.e., below the lower limit of quantification [LLOQ]) or "> x" (i.e., above the upper limit of quantification [ULOQ]) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings.

4.4 Software

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment.

4.5 Analysis Sets

Details of the analysis sets are presented in Table 2.

Table 2 Analysis Sets

Analysis set	Description
Enrolled	All patients who sign the ICF.
Safety	All patients who receive any amount of study treatment.

Analysis set	Description
	Safety data will be 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).
* 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

Upon database release, protocol deviations and analysis set outputs will be produced and will be sent to AZ for review. Prior to database lock for the final analysis, an analysis set classification meeting will be arranged to discuss the outputs and to decide which patients and/or patient data will be excluded from certain analyses. Decisions made regarding the exclusion of patients and/or patient data from analyses will be made prior to database hard lock for the final analysis and will be documented and approved by AZ.

A summary on which analysis set will be used for each outcome variable is provided in Table 3.

Table 3 Summary of outcome variables and analysis sets

Outcome variable	Analysis Sets
Study population/Demography Data	
Disposition of patients	Enrolled
Demography characteristics	Safety
Baseline and disease characteristics	Safety
Important protocol deviations	Enrolled
Medical History	Safety
Prior anti-lymphoma therapy	Safety
Concomitant Medication	Safety
Subsequent anti-lymphoma therapy	Safety
Efficacy Data	
ORR	Response evaluable
DoR	Response evaluable
TTR	Response evaluable

Outcome variable	Analysis Sets
OS	Safety
PFS	Safety
TFST	Safety
Safety data	
Exposure	Safety
AEs	Safety
Laboratory measurements	Safety
Vital Signs	Safety
ECGs	Safety
Pharmacokinetics	
Pharmacokinetic variables	PK
Patient-reported Outcome Data	
EORTC QLQ-C30, PRO-CTCAE, PGI-TT	Safety

DoR duration of response; ORR objective response rate; OS overall survival; PFS progression free survival; PK pharmacokinetic; TFST: time to first subsequent therapy or death; TTR: time to objective response.

4.6 Study Patients

4.6.1 Disposition of Patients

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion.

Patient disposition including screen failures and reason for screen failure will be summarised and listed based on all subjects enrolled/screened (i.e. informed consent received) by cohort.

Summaries will include the number and percentage of patients:

- Patients enrolled /screened (informed consent received)
- Screen failures
- Patients assigned to treatment
- Patients assigned to treatment , but who were not treated
- Patients ongoing in study at data cut-off (DCO)
- Patients ongoing treatment at DCO
- Patients who discontinued treatment

- Patients who discontinued study

A breakdown of the primary reason for discontinuation treatment and/or study will be presented for all patients.

Subject discontinuation will be listed, including description of cohort, disposition terms, date, and total treatment duration (days) derived as described in section 4.12.1.

The number of patients recruited in each country will be presented by cohort.

Patients who withdraw from study due to COVID-19 will be presented separately. Study disruptions due to the COVID-19 will also be presented. Listings for patients affected by COVID-19 will also be presented.

The analysis sets will be summarised by cohort and overall. Any exclusions from analysis sets will be listed.

4.6.2 Protocol Deviations

Important protocol deviations (IPDs) are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments.

This assessment will be performed at a Data Review Meeting (DRM) shortly before database lock. Results and population assignments will be summarized in a DRM report which will be signed off by Parexel Lead Biostatistician, PM , AZ Global Product Statistician and AZ Physician.

Important protocol deviations and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

IPDs will be listed and summarised by cohort and overall for Enrolled Analysis Set. Important protocol deviations related to COVID-19 will be summarized separately.

A full list of protocol deviations can be found in the study-specific Protocol Deviation Specification.

4.7 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarised and listed for all patients in the Safety Analysis Set by cohort:

- Demographic characteristics (age[years], age group [⩾ 18-< 64; ⩾ 65], sex [female; male], race, ethnicity).
- Patient characteristics at baseline (height[cm], weight [kg], and body mass index [BMI] [kg/m^2]).
- Disease stage (I, II, III, IV) at study entry.
- Presence of bulky disease (Y/N) [Bulky disease is defined as the presence of a single lesion with largest diameter being 7 cm or larger. The presence of bulky disease will be determined by the investigator when baseline disease extent is evaluated]
- Bone marrow involvement, yes (%)
- Other extranodal involvement, yes (%)
- Prior exposure to CART therapy, yes (%)
- Prior exposure to PI3K, yes (%)
- Prior autologous stem cell transplant (auto HSCT), yes (%)
- Prior allogenic stem cell transplant (allo HSCT), yes (%)
- Prior bispecifics, yes (%) (as identified during physician reviewed before DCO date)
- Disease Status at study entry
    - Relapsed after the last line of therapy (i.e BOR to last line is CR or PR, followed by relapse), n %
        - Relapsed <6 months from completion of last line of therapy, n %
    - Refractory to last line of therapy (i.e. BOR to last line is SD or PD) n, %
- Time from diagnosis to study treatment calculated as (date of study entry – date of initial diagnosis) / 365.25

Prior bispecifics TCEs and/or preferred drug codes already provided.

FL, Cohort 1A

- Histological Grade (Grade 1, 2, 3A)
- FLIPI score High (≥3), Intermediate (2), Low (0,1)
- FLIPI-2 score High (≥3), Intermediate (2), Low (0,1)
- High tumour burden per GELF criteria, yes (%)
- Progression of disease within 2 years (POD24), yes (%)
- Double Refractory (refractory to both anti-CD20mAb and alkylating agent), yes (%)

POD24 is defined as relapse within 24 months from completion of first line therapy;
POD24 (months)= (date of PD First Regimen-First line – Stop date of first line of therapy+1) /(365.25/12).

Double refractory will be derived by selecting the patients with a BOR or either PD/SD following an anti-CD20 mAb or and alkylating agent in any of the prior lines.

MZL, Cohort 1B

- MZL subtypes: nodal, extranodal/MALT, splenic, n %

MCL, Cohort 1C

- MCL histological variants: blastoid vs other
- t (11; 14) or Cyclin D1 overexpression, yes (%)
- TP53 alteration
- Simplified Mantle Cell Lymphoma International Prognostic Index (s-MIPI) high vs intermediate/low
- Reason for BTK (Bruton's tyrosine kinase) discontinuation (PD vs toxicity/other)

A comprehensive review of all investigational BTK agents will be performed by AZ. AZ will provide a list with ATC categories to identify the participants who discontinued BTK as described above.

4.8 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA). All medical history (past and current) will be listed and the number and percentage of patients with any medical history will be summarised for the safety analysis set by system organ class (SOC) and preferred term (PT) separate for each cohort.

4.9 Prior Anti-lymphoma Therapy

Prior cancer surgery will be listed and summarised similarly to Medical History.

Prior anti-lymphoma drugs will be summarized using frequency tabulations by ATC classification and generic drug name (World Health Organization [WHO] dictionary term).

The following summaries will be produced by cohort using the safety analysis set:

- Number of prior lines
- Previous cancer therapies

4.10 Concomitant Medications and Other Treatments

Information on any concomitant treatment, procedures, or other medication considered necessary by the investigator for patient´s safety and wellbeing (including supportive care e.g. transfusions and vaccines) that the patient is receiving within 4 weeks prior to first dose of study treatment or receives

during the study including 30-day follow up period following the last dose if study treatment must be recorded in the eCRF along with reason for use.

Treatments received prior to, concomitantly, or post-treatment will be coded using the Word Health Organisation (WHO) Drug Dictionary (WHODD) Anatomical Therapeutic Chemical (ATC) classification codes. Concomitant medications will be summarised for the safety analysis set by ATC classification codes.

For the purpose of inclusion in prior and/or concomitant medication summaries, incomplete medication start and stop dates will be imputed as detailed in Section 4.3.3.1.

Prior medications, concomitant and post-treatment medications are defined based on imputed start and stop dates as follows:

- Prior medications are those taken prior to study treatment with a stop date prior to first dose of study treatment.
- Concomitant medications are those with a stop date on or after the first dose date of study treatment (and could have started prior to or during treatment).
- Post treatment medications are those with a start date after the last dose date of study treatment.

Concomitant medication summary will be produced by cohort using the safety analysis set.

All prior, concomitant and medication and post study treatment medication data will be listed.

Missing coding terms should be listed and summarised as “Not coded”.

4.11 Efficacy Evaluation

4.11.1 Analysis and Data Conventions

Module 1:

Each cohort will be analysed separately for the primary, secondary and safety endpoints.

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

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

H0: ORR = 25% versus

H1: ORR = 40%.

4.11.1.1 Multi-centre Studies

No adjustments for centre will be performed in this study.

4.11.1.2 Adjustments for Covariates

No adjustments for covariates will be performed.

4.11.1.3 Handling of Dropouts or Missing Data

Summary statistics will be based on non-missing values unless otherwise specified.

4.11.1.4 Multiple Comparisons/Multiplicity

There will be no formal adjustment for multiplicity.

4.11.1.5 Blinded Independent Central Review (BICR)-Module 1

A Blinded Independent Central Review comprised of independent experts will support primary endpoint (ORR) and secondary endpoints (DOR, PFS, TTR).

Full details on the BICR procedures and processes can be found in the BICR Charter.

4.11.1.6 Efficacy Interim Analyses

Descriptive summaries and the analysis methods for the outputs required for the interim analysis will follow the methodology outlined in this SAP. The list of tables, listings and figures required for interim analysis will be prepared as per AZ standards; and they will be flagged in the list of TLFs.

Due to early termination of the study, the Efficacy Interim Analyses will not be conducted.

Module 1:
Cohort 1A (FL) and Cohort 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 with capivasertib monotherapy 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.

CCI

CCI

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.

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%.

CCI

CCI

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.

4.11.1.7 Examination of Subgroups

The following subgroup analysis will be performed for ORR (the primary efficacy variable) by comparing ORR in the following groups:

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

- Age at screening (< 65 years versus ≥ 65 years)
- Relapsed versus Refractory
- Prior lines of therapy (2 versus ≥3)
- Prior CART (yes/no)
- Prior bispecific TCE (yes/no)
- Prior PI3K inhibitor (yes/no)
- Prior HSCT (yes/no)
- Bulky disease (yes/no)
- FLIPI (low/intermediate versus high)
- GELF (yes/no)

For Cohort 1B (MZL) a summary table of ORR according to MZL subtype will be produced.

Cohort 1C (MCL)

- Age at screening (< 65 years versus ≥ 65 years)
- Relapsed versus Refractory
- Prior lines of therapy (2 versus ≥3)
- Prior CART (yes/no)
- Prior bispecific TCE (yes/no)
- Prior HSCT (yes/no)
- Bulky disease (yes/no)
- MIPI (low/intermediate versus high)
- Prior BTK discontinued for PD /Prior BTK discontinued for AE/other

In addition, the ORR estimate with its 95% CI will be presented graphically on a forest plot for each component of each subgroup.

Due to early termination of the study, subgroup analysis will not be conducted.

4.11.2 Primary Efficacy Variable – Objective response rate

ORR is the primary efficacy variable for Module 1.

The ORR is defined as the proportion of patients who achieve either complete response (CR) or partial response (PR) as best response as determined by blinded independent central review (BICR) per Lugano 2014 criteria prior to any evidence of progression 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 best response as assessed by the investigator and will be based on 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 discontinue study treatment without a response or progression, receive a subsequent anti-lymphoma therapy and then respond will not be included as responders in the ORR (i.e. the visit contributing to a response must be prior to subsequent therapy for the patient to be considered as a responder).

The ORR will be based on the BICR Lugano data and using all scans regardless of whether they were scheduled or not.

Measurable disease at baseline is defined as 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

Summaries will be produced to present the number and percentage of patients with a response (CR/PR) based upon the number of patients with measurable disease at baseline per BICR. ORR will be calculated and binomial exact confidence intervals at 95% will be presented for patients in the response evaluable analysis set.

Summary showing concordance between BICR and investigator´s assessments may be presented. The concordance rate is the number of patients that are concordant over the total number of patients assessed. The patients are concordant when the investigator and BICR conclude the same response assessment for a patient.

Best objective response (BoR)

BoR is calculated based on the overall visit responses recorded in the BICR dataset. It is the best response a patient has had following enrolment, but prior to starting any subsequent anti-lymphoma therapy and up to and including Lugano progression or the latest evaluable assessment in the absence of Lugano progression. Categories of BoR will be based on Lugano criteria using the following response categories: CR, PR, SD, PD, not evaluable (NE) and unknown.
BoR will be summarised by number of patients and percentage for each category (CR, PR, SD, PD and NE). No formal statistical analyses are planned for BoR.

Tumour assessments

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 for response assessment (refer to Appendix I of CSP).

The change in tumour burden, as measured by the sum of the product of the perpendicular diameters (SPD) of the selected lesions (reported as target lesions), from baseline to post-baseline nadir will be summarized in absolute numbers (cm2) and percentage. A graphical summary of the best percentage change in the target lesion tumor size will be presented in a vertical bar chart with each patient's best

percent change from baseline to nadir displayed as a vertical bar, with color coding that indicates best response attained ("waterfall" plot). Only patients included in the response evaluable analysis set with at least one post-baseline radiographic assessment (e.g. CT scan) will be included in the waterfall plot. Spider plots of tumour burden change over time will be presented. Only patients with measurable disease will be included in summaries.

The following tumour assessments details for NHL will be collected and listed by patient:

- Target lesion size
- Non-target lesion
- New lesion
- Spleen/Liver Disease
- Overall disease response
- Split target lesion

4.11.3 Secondary Efficacy Variables

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

4.11.3.1 Duration of Response (DoR)

DoR is a secondary efficacy variable for Module 1.

DoR is defined as the time from the date of first documented objective response (CR or PR) until date of documented disease progression per Lugano classification or death (by any cause in the absence of disease progression).

DoR (months) = (date of PFS event [progression/death] or censoring – date of first objective response + 1) / (365.25/12).

The end of response should coincide with the 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. If a patient does not progress following a response, then their DoR is censored on the PFS censoring date. Only patients who have achieved objective response (CR or PR) are evaluated for DoR

The analysis will include all patients in the response evaluable analysis set who had response, regardless of whether the subject withdraws from therapy. Patients who had the event after the start of subsequent therapy, or are progression free and alive at the time of data cut-off, or have unknown status will be censored at the last tumour assessment on or before the start of subsequent therapy.

Descriptive data will be provided for the DoR in responding patients, including the associated

Kaplan Meier curves, medians (utilising Kaplan-Meier methodology) and corresponding 95% CIs. DoR will be calculated by KM estimates with 95% CI and presented. In addition, the percentage of patients remaining in response at 3, 6, 12 and 18 months after initial response will also be presented. Swimmer plots that clearly show the profile of each patient who responds will also be produced.

4.11.3.2 Progression-free Survival (PFS)

PFS is a secondary efficacy variable for Module 1.

PFS is defined as the time from date of first dose until documented disease progression, as assessed by investigator/BICR, or death from 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 Lugano progression. Patients who had the event after the start of subsequent therapy, or who are progression free and alive at the time of data cutoff,or have unknown status will be censored at the time of their last disease assessment on or before the data cutoff. Subjects with no post-baseline disease assessment will be censored on Day 1. The PFS time will always be derived based on the scan/assessment dates and not visit dates.

PFS (months) = (date of PFS event [progression/death] or censoring – date of first dose + 1) / (365.25/12).

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 (utilising Kaplan-Meier methodology), 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.

A summary of censoring rules and the date of PD/death or censoring are given in Table 4. Note that censoring overrides event in certain specified cases and that this table does not indicate the order for programming,

Table 4 Summary of Censoring Rules for PFS

Situation	Date of PD/Death or Censoring	PFS Outcome
Documented Progressive Disease (PD) or death in the absence of progression	Date of earliest documentation of PD or date of death in the absence of progression	Event
Either no assessment at baseline or no evaluable assessments post-baseline AND death prior to second scheduled post-baseline disease assessment	Date of death	Event
Either no assessment at baseline or no evaluable assessments post-baseline AND no death prior to second scheduled post-baseline disease assessment	Date of first dose (Day 1)	Censored
PD or death (in the absence of progression) immediately after ≥ 2 consecutive missed disease assessments as per the protocol specified assessment schedule	Last evaluable progression-free disease assessment prior to missed assessments	Censored
On-going with neither PD nor death at the time of analysis or lost to follow-up or withdrawn consent	Date of last evaluable disease assessment	Censored
Initiation of subsequent anti-cancer therapy prior to PD or death	Date of last evaluable disease assessment prior to initiation of subsequent anti-cancer therapy	Censored for sensitivity analysis only

Abbreviations: PD, progressive disease; PFS, progression-free survival

In addition, the number of patients prematurely censored will be summarised. A patient would be defined as prematurely censored if they had not progressed (or died in the absence of progression) and the last scan prior to DCO was more than one scheduled Lugano assessment interval plus 2 weeks prior to the DCO date.

Additionally, summary statistics will be given for the number of days from censoring to DCO for all censored patients.

A summary of the duration of treatment will be summarised using median time from first dose to date of censoring (date last known to not have progressed) in censored (not progressed) patients only.

Additionally, summary statistics for the number of weeks between the time of progression and the last Lugano assessment prior to progression will be presented.

All collected Lugano data will be listed for all dosed patients.

A sensitivity analysis will be conducted to assess the potential impact of COVID-19 related deaths

on PFS. That is patients who had a PFS event due to death where the primary or secondary cause of death was COVID-19 infection or COVID-19 infection was reported as a fatal AE, will be censored at the last available Lugano assessment prior to COVID-19 infection related death.

4.11.3.3 Overall Survival (OS)

OS is a secondary efficacy endpoint for Module 1.

OS is defined as the time from date of first dose until the date of death from any cause.

OS (months) = (date of death or censoring – date of first dose + 1) / (365.25/12).

The analysis will include all dosed patients, regardless of whether the patient withdraws from treatment or receives another anti-lymphoma therapy. Patients who have not died by the analysis DCO date will be censored at their last date known to be alive before the DCO date. Patients known to be alive or dead after the DCO date will be censored at the DCO date. Patients lost to follow-up will be censored at the date the patient is last known to have been alive.

Survival follow-up phone calls will be made in the weeks 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. The status of ongoing, withdrawn (from study) and "lost to follow-up" patients at the time of final OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is applicable to do so under applicable local laws.

For any OS analysis performed prior to the final OS analysis, in the absence of survival calls being made, it is necessary to use all relevant eCRF fields to determine the last recorded date on which the patient was known to be alive for those patients still on treatment.

If a patient is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last date known to be alive + 1 from the database and the death date using the available information provided:

- For missing day only – using the 1st of the month
- For missing day and month – using the 1st of January

If there is evidence of death, but the date is entirely missing, it will be treated as missing, i.e., censored at the last known date alive.

Kaplan-Meier plots of OS will be presented. Summaries of the number and percentage of patients experiencing an OS event will be provided along with the median OS (utilising Kaplan-Meier

methodology), its 95% CI, and the proportion of patients who were known to be alive at 6 months, 12 months and 18 months.

A sensitivity analysis will be conducted to assess the impact of COVID-19 related deaths on OS. That is, patients who had a death event where the primary or secondary cause of death was COVID-19 infection or COVID-19 infection was reported as a fatal AE, will be censored at the date of their COVID-19 infection related death.

The number of patients prematurely censored will be summarised. A patient would be defined as prematurely censored if there is no indication that the patient died, but there is no survival available in the 13 weeks prior to the DCO.

Due to early termination of the study, the sensitivity analysis will not be conducted.

4.11.3.4 Time to First Subsequent Therapy or Death (TFST)

TFST is a secondary efficacy endpoint for Module 1.

TFST is defined as time from date of first dose until the start date of subsequent anti-lymphoma therapy (including local radiotherapy) 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.

TFST (months) = (date of subsequent anti-lymphoma therapy – date of dose + 1) / (365.25/12).

TFST will be summarised using Kaplan-Meier methodology. Same methodology as for PFS will be used.

Due to early termination of the study, TFST is not presented.

4.11.3.5 Time to Objective Response (TTR)

TTR is a secondary efficacy endpoint for Module 1.

TTR is defined as the time from the date of first dose until the date of first documented objective response per Lugano classification as assessed by BICR. The analysis will include all patients in the response evaluable analysis set who had a response.

TTR (months) = (date of first objective response – date of first dose + 1) / (365.25/12).

The TTR will be summarised (ie, number of subjects [%] based upon the number of patients with CR or PR) by time point that the response was first observed. Descriptive data (i.e., median and quartiles) will be provided for TTR in responding subjects (utilising Kaplan-Meier methodology), including the

associated Kaplan Meier curves, and corresponding 95% CIs.

4.11.4 Pharmacokinetics

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

The PK data from this study may be pooled with data from other studies for population PK and exposure-response analyses. The results from such analyses will be reported separately.

4.11.4.1 Pharmacokinetic Concentrations

Plasma concentrations of capivasertib will be listed by patient and time-point.

Plasma concentrations will be summarised by cohort and scheduled time point using the following descriptive statistics, based on the PK analysis set:

- n
- n below LLOQ
- geometric mean (gmean)
- geometric coefficient of variance (%) (gCV)
- arithmetic mean (mean)
- arithmetic standard deviation (Std Dev)
- median
- minimum (min)
- maximum (max)

The gmean is calculated as exp(μ), where μ is the mean of the data on the natural log scale.
The gCV is calculated as 100 x sqrt[exp(s^2)-1], where s is the Std Dev of the data on the natural log scale.

Handling of Non-Quantifiable Concentrations
Individual concentrations below the LLOQ of the bioanalytical assay are reported as NQ in the listings with the LLOQ defined in the footnotes of the relevant Table/Listing. Individual plasma concentrations that are Not Reportable are reported as NR and those that are missing are reported as NS (No Sample) in the listing. Plasma concentrations that are NQ, NR or NS are handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS are excluded from the summary table.
- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values are set to the LLOQ, and all descriptive statistics are calculated accordingly.
- At a time point where more than 50% (but not all) of the values are NQ, the gmean and gCV% are set to Not calculable (NC). The maximum value is reported from the individual data, and the minimum and median are set to NQ.

- If all concentrations are NQ at a time point, no descriptive statistics are calculated for that time point. The gmean, minimum, median and maximum are reported as NQ and the gCV% as NC.

Three observations > LLOQ are required as a minimum for a plasma concentration to be summarised. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

Precision and Rounding Rules for Pharmacokinetic Data

PK concentration data
PK concentration data listings present to the same number of significant figures as the data received from the bioanalytical laboratory (usually but not always to 3 significant figures) and against the same units as received.

PK concentration descriptive statistics present 4 significant figures with the exception of the min and max which present 3 significant figures and n and n<LLOQ which present as integers.

4.11.5 B Symptoms

Information on B symptoms (unintentional weight loss within previous 6 months, fevers > 38 C, night sweats, significant fatigue) will be listed for all patients and visits.

4.12 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Analysis Set and presented by cohort.

Safety analysis across all modules in this study will be analysed in a similar fashion as described below.

4.12.1 Extent of Exposure

Module 1
Exposure data will be summarised and listed for safety analysis set.
Duration of exposure is defined as:

1. Total treatment duration = (min (last dose date where dose > 0 mg, date of death, date of DCO) − date of first dose +1).
2. Actual treatment duration = total treatment duration-total duration of dose interruptions, where the total duration of dose interruption is defined as any length of time where the patient has not taken any of the planned doses.

For handling exposure and dose interruptions, the following rules will be considered.

If a patient permanently discontinues study treatment during a dose interruption, then the date of last administration of study medication recorded on the eCRF will be used in the programming.

Total dose of capivasertib will be calculated as the sum of all doses received during the study.

The duration of an interruption will be calculated as [date/time treatment resumed – date/time treatment stopped+1]. Overall duration of interruption will be determined as the sum of all individual interruptions during the study for a particular patient. Duration of dose interruption is defined as any length of time where the participant has not taken any of the planned doses; after four days of dosing patients are covered by the drug for an additional three days before having to take drug again. Missed or forgotten doses will not be included as dose interruptions in the summary tables but the information appears in the listing for dosing. However, these missed and forgotten doses will be considered in the derivation of actual exposure.

Dose intensity of capivasertib will be addressed by considering relative dose intensity (RDI). RDI is the percentage of the actual dose delivered relative to the intended dose up to treatment discontinuation. RDI will be defined as:

RDI(%)= 100 *d/D,

where:
d is the actual cumulative dose delivered up to the last day of dosing,
and
D is the intended cumulative dose up to the last day of dosing (ie, that would have been delivered without a modification of the dose or schedule).

Planned total dose will be defined as total dose of capivasertib that would have been delivered if there were no modification to dose.

Actual total dose will be defined as the sum of all doses received during the study per patient.

The following summaries will be produced:

- Summary of interruptions and reductions of study treatment
- Summary of RDI
- Summary of intended and actual exposure of capivasertib
- Summary of total dose

4.12.2 Duration on study

Duration of follow-up (months)= (min (date of death, date of DCO, study end date, date of withdrawal) – randomization date/date of first dose +1) / (365.25/12)

Summary statistics will be provided for duration on study.

4.12.3 Adverse Events

Adverse events (AEs) and serious AEs (SAEs) will be collected from the time of signing of the informed consent throughout the treatment period and including the follow-up.

AEs will be coded using the latest or current Medical Dictionary for Regulatory Activities (MedDRA) version. AEs will be graded according to the National Cancer Institute of Common Terminology Criteria for AEs (CTCAE version 5.0).

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.

These AESIs will be identified as a list of categories provided by the patient safety team.

Reviews will take place prior to database lock to determine whether any AE should be classified as AESIs. The review will identify which higher-level terms, and which preferred terms should contribute to each AESI.

The following are considered to be AESIs:
- Hyperglycaemia
- Non-infectious diarrhoea
- Infective pneumonia
- Rash
- Stomatitis
- QT Prolongation
- Haematological effects

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+7 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 +7 days after last dose of study treatment or up to the day prior to start of subsequent therapy.

Unless otherwise stated, only AEs defined as treatment emergent will be included in the summary tables. Adverse events not classified as treatment emergent will only be listed.

All reported AEs will be listed along with the actual treatment received, cohort, study day of start, duration of event, CTCAE grade, relationship to study treatment, seriousness, action taken and outcome. Frequencies and percentages of patients reporting each preferred term will be presented (i.e., multiple events per patient will not be accounted for, except for event level summaries).

Summary information (the number and percentage of patients by treatment) by MedDRA SOC and PT will be tabulated for:

- All AEs
- All AEs causally related to capivasertib (as determined by the reporting investigator)
- AEs of CTCAE grade 3 or higher
- AEs of CTCAE grade 3 or higher, causally related to capivasertib (as determined by the reporting investigator)
- AEs with outcome of death
- AEs with outcome of death, causally related capivasertib (as determined by the reporting investigator)
- AE leading to dose reduction of capivasertib
- AEs leading to dose interruption of capivasertib
- All SAEs
- All SAEs causally related to capivasertib (as determined by the reporting investigator)
- AEs leading to discontinuation of capivasertib
- AEs leading to discontinuation of treatment, causally related to capivasertib (as determined by the reporting investigator)
- SAEs leading to discontinuation of capivasertib
- SAEs leading to discontinuation of treatment, causally related to capivasertib (as determined by the reporting investigator)
- AESIs

An overall summary of the number and percentage of patients in each of the above categories will be presented, as well as an overall summary of number of events in each of the above categories. In addition, a table of most common AESIs, showing all events that occur in at least 2 of patients will be summarized by PT, by decreasing frequency.

In addition, an event level summary will be presented for all AEs by PT.

Summaries of the number and percentage of patients with AEs will also be produced by maximum reported CTCAE grades, SOC, and PT and of most common AEs of CTCAE grade 3 or higher by SOC and PT.

Summaries of the number and percentage of patients with AEs will also be produced by maximum reported CTCAE grades, SOC, and PT and of most common AEs of CTCAE grade 3 or higher by SOC and PT.

For diarrhoea events, the overall summary for all AEs reporting the number and percentage of patients in each category (e.g. any diarrhoea AE possibly relatedto capivasertib) will be repeated for diarrhoea events.

For diarrhoea events the number of patients with any diarrhoea AE occurring only on dosing days and occurring only on off days .

In addition, AEs with outcome death, SAEs, AEs leading to discontinuation of treatment and AEs leading to treatment delay and AESIs will be listed separately.

The following additional summaries will be presented should more than 2% of the patients treated in this study have COVID-19 infection:

- All AEs, excluding AEs associated with COVID-19 infection
- All AEs associated with COVID-19 infection
- AEs with outcome of death, excluding AEs associated with COVID-19 infection
- AEs associated with COVID-19 infection with outcome of death
- AEs leading to discontinuation of study intervention, excluding AEs associated with COVID-19 infection
- AEs associated with COVID-19 infection leading to discontinuation of study intervention

The above categories will also be included in the overall AE summaries.

Further COVID-19 related summaries related to AEs may be added if required.

In addition, summaries of treatment emergent AESIs will be presented by maximum reported CTCAE grade, by AE outcome, including time of resolution (on-treatment or follow-up), whether treatment was received (yes/no) and action taken.

Descriptive statistics for time to onset and duration of first AESI for patients experiencing AESIs will be presented. Time to onset will be derived as [AESI start date – Treatment start date + 1] while duration will be derived as [AESI end date – AESI start date + 1]. If the AESI is ongoing at the respective DCO, the DCO date will be imputed as the end date for duration calculations. Time to onset and duration will be presented in days.

The following characteristics of diarrhoea AEs will also be summarised separately for

events on dosing days and on off dosing days:
• Duration of events for on dosing days only (days)
• Pattern of event (intermittent / continuous)
• Duration of CTCAE grade 3 diarrhoea (days)

4.12.4 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.

Any dose, or frequency of dosing, that exceeds this dose regimen will be reported as an overdose.

A summary of overdose will be provided with the number and percentage of patients categorised as:

- Number of patients with an overdose associated with an AE.
- Number of overdoses per patient.
- Frequencies of overdose, n (%).
- Time to first overdose (weeks).

Due to early termination of the study, Overdose is not presented.

4.12.5 Deaths

A summary of deaths will be provided with the number and percentage of patients categorised as:

- Total number of deaths
  - Related to disease under investigation only
  - AE outcome of death only
  - AE with outcome of death only and onset date <= 30 days + 7 days after last dose of study treatment
  - Other deaths

A corresponding listing will also be produced.

Due to early termination of the study, Deaths are listed only.

4.12.6 Clinical Laboratory Evaluation

All local laboratory results collected will be listed.

Summaries for safety laboratory will only include the parameters specified in Table .

Table 5 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry**
	B-Glycosylated haemoglobin (HbA1c) (fasting)
B-Haemoglobin (Hb)	S/P-Creatinine
	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
	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.

NB. In case a patient shows an AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix E of CSP '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.

All values will be classified as low (below range), normal (within range), or high (above range) based on local laboratory reference ranges. Results will be converted to standard units. For assessments included in CTCAE version 5.0, the CTCAE grade will be calculated.

All clinical laboratory results will be listed.

For all continuous laboratory assessments, absolute value and change from baseline will be summarised using descriptive statistics at each scheduled assessment time by cohort.

For clinical chemistry and haematology, shift tables will present movements from baseline to maximum and minimum values on-treatment according to reference range classification. CTCAE grade changes from baseline to the maximum grade on-treatment will also be provided. Corresponding shift tables ("Negative", "Trace", "Positive", "0", "+", "++", "+++") will be produced for urinalysis.

Due to early termination of the study, minimum shift tables, and CTCAE grade changes not presented.
Due to early termination of the study, Urinalysis is not presented.

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

Plots for both maximum post-baseline alanine transaminase (ALT) and aspartate transaminase (AST) versus the maximum post-baseline total bilirubin (expressed as multiples of their upper limit of normal [ULN] reference range) will be produced with reference lines at 3 x ULN for ALT and AST and 2 x ULN for total bilirubin. Box plots of absolute values and change from baseline values for all haematology and clinical chemistry parameters will also be presented.

Liver biochemistry test results over time for patients who show elevated ALT or AST (≥ 3 x ULN) and elevated bilirubin (≥ 2 x ULN) (elevated results do not need to be present at the same visit) or ALT or AST of ≥ 5 x ULN, will be tabulated and plotted.

Due to early termination of the study, ALT and AST plots are not presented.
Due to early termination of the study, box plots of change from baseline are not presented.
Due to early termination of the study, Liver biochemistry results over time are tabulated only.

4.12.7 Vital Signs and Weight

The following vital signs will be assessed and listed:

- Systolic blood pressure (SBP) [mmHg].
- Diastolic blood pressure (DBP) [mmHg].
- Pulse rate (bpm).
- Pulse oxygen saturation (%)

- Oral body temperature (°C).
- Weight (kg)

Vital signs data described above will be listed by patient and timepoint including reference range indicator for measurements that are outside the reference range (low, normal, high).

Change from baseline in vital signs parameters will be calculated for each post-baseline visit. Descriptive statistics for absolute values and changes from baseline will be presented for pulse, systolic and diastolic blood pressure, body temperature and weight by cohort.

A shift table of baseline to maximum and minimum value on treatment for blood pressure and pulse will also be presented using the normal ranges in Table .

Table 6 Vital Sign Normal Ranges

Vital Sign	Outside AZ defined reference range lower limit if	Outside AZ defined reference range upper limit if	Treatment emergent decrease if	Treatment emergent increase if
Systolic blood pressure (mmHg)	< 90	> 140	< -20	> 20
Diastolic blood pressure (mmHg)	< 50	> 90	< -10	> 10
Pulse (bpm)	< 50	> 100	< -20	> 10

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.

In addition, box plots of absolute values and change from baseline in blood pressure, pulse, body temperature and weight will also be presented.

Due to early termination of the study, shift tables are not presented.
Due to early termination of the study, box plots of change from baseline are not presented.

4.12.8 Electrocardiogram

The following parameters will be assessed in 12-lead ECGs:

PR-interval (msec).

QRS-duration (msec).

RR-interval (msec).

QT-interval (msec).

QT-interval corrected using the Fridericia correction formula (QTcF) (msec).

Heart rate (beats per minute [bpm]).

All ECGs will be conducted as triplicate measurements. The average of the three measurements will be used in summaries and data listings. If one measurement is missing the average of the two measurements will be used. If there is only one measurement, this will be used in the summary table. ECG parameters will be listed by patient including changes from baseline for numeric ECG parameters. The individual measurements will be displayed in the data listings.

Descriptive statistics for absolute values and changes from baseline will be presented by cohort.

QTcF outliers (defined as values following study treatment that are greater than 450 msec or increases from baseline greater than 30 msec) will be summarised using cumulative counts and percentages under the following categories:

- Absolute value > 450 msec
- Absolute value > 480 msec
- Absolute value > 500 msec
- Change from baseline > 30 msec
- Change from baseline > 60 msec
- Change from baseline > 90 msec
- Absolute value > 450 msec and change from baseline > 30 msec
- Absolute value > 500 msec and change from baseline > 60 msec

All ECG data received will be presented in data listings.

For each scheduled post-baseline assessment, descriptive statistics for all ECG parameters will be presented for observed values and change from baseline.
Overall evaluation on of ECG results will be summarised descriptively. 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.
Box plots of absolute values and change from baseline in ECG parameters over time will be presented.

Shift table from baseline to maximum and minimum value on-treatment will be presented using the normal ranges in Table .

Due to early termination of the study, shift tables are not presented.

Table 7 ECG Normal Ranges

ECG Parameter	Outside AZ defined reference range lower limit if	Outside AZ defined reference range upper limit if
Heart rate (bpm)	< 40	> 100
RR (msec)	< 600	> 1200
PR (msec)	< 120	> 200
QRS (msec)	< 60	> 109
QT (msec) and QTcF (msec)	< 320	> 450

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.

4.12.9 Eastern Cooperative Oncology Group performance status (ECOG PS)

The ECOG performance status will be listed and summarised as frequency counts by cohort.

4.12.10Echocardiogram (ECHO)/ MUGA Scan

All echocardiogram data received will be presented in data listings.

Left Ventricular Ejection Fraction will be assessed at screening and thereafter as clinically indicated. A listing of LVEF by visit will be presented

4.12.11 Safety Interim Analysis-Module 1

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

The patient disposition, demographic characteristics, baseline patient and disease characteristics, exposure, baseline and post-baseline safety parameters (AEs, clinical laboratory assessments, vital signs and ECG data) will be summarised by cohort (Cohort 1A, Cohort 1B, Cohort 1A+1B, Cohort 1C). Preliminary efficacy data based on investigator responses may also be included.

Descriptive summaries and the analysis methods for the outputs required for the interim analysis will follow the methodology outlined in this SAP.

The list of tables, listings and figures required for safety interim analysis will be prepared as per AZ standards; and they will be flagged in the list of TLFs.

Due to early termination of the study, the Safety Interim Analyses will not be conducted.

4.13 Other Analyses

4.13.1 Patient-reported Outcome (PRO)

PRO data assessed using the following measures:

- EORTC QLQ-C30
- PRO-CTCAE
- PGI-TT

Will be analysed by descriptive summaries and graphic presentations. The analyses will be based on all dosed patients. Missing data will not be imputed and the analyses will be based on observed non-missing data.

Due to early termination of the study, PRO will not be presented.

4.13.1.1 EORTC QLQ-C30

The EORTC-QLQ-C30 was developed to assess the health-related quality of life of cancer patients participating in international clinical trials.

The EORTC QLQ-C30 consists of 30 questions, which can be grouped to produce five multi-item functional scales, three multi-item symptom scales, six individual items (five items assessing additional symptoms commonly reported by cancer patients and one item on the financial impact of the disease) and a two-item global measure of health status/quality of life. For further details refer to EORTC-QLC-C30 scoring manual

The global health status/ QoL, functional scales and symptom scales, including the items included in each of these scales are presented in Table .

Table 8 Scoring the QLQ-C30

	Scale	Number of Items	Item Range [a]	Item Numbers
Global Health Status/QoL				
Global Health Status	QL2	2	6	29, 30
Functional Scales				
Physical functioning	PF2	5	3	1 to 5
Role functioning	RF2	2	3	6, 7
Emotional functioning	EF	4	3	21 to 24
Cognitive functioning	CF	2	3	20, 25
Social functioning	SF	2	3	26, 27
Symptom Scales/ Items				
Fatigue	FA	3	3	10, 12, 18
Nausea and vomiting	NV	2	3	14, 15
Pain	PA	2	3	9, 19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhoea	DI	1	3	17
Financial difficulties	FI	1	3	28

[a] Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.

Descriptive statistics for subscale scores, including changes from baseline will be presented by time point and cohort. Plots of mean change from baseline in total and subscale scores over time will also be presented with indicators for the number of patients at each visit.

CCI [redacted] Other methods including distribution-based methods, cumulative distribution function, and probability density function curves, and methods using other anchors may also be considered. Once the clinically meaningful change thresholds are established, time to deterioration analyses and proportion of patients with deteriorated, stable and improved EORTC QLQ-C30 scores will also be explored. These analyses will be conducted separately and the detailed methodology will be described in a separate PRO SAP.

4.13.1.2 PRO-CTCAE

PRO-CTCAE data will be summarised descriptively in each cohort for each patient-reported symptomatic AE item. The summary will include

1. Number and proportion of patients reporting different levels of symptomatic AE at each time point
2. Number and proportion of the worst response option reported by patients within 24 weeks
3. Number and proportion of patients who report the presence of the symptom at baseline
4. Number and proportion of patients who report any worsening from baseline within 24 weeks
5. Number and proportion of patients who worsen from a score <4 (on a 0 – 5 scale) at baseline to a score 4 or 5 within 24 weeks.

Some symptomatic AEs may have multiple attributes (frequency, interference, severity, presence/absence), and the analyses above will be applied to each attribute.

4.13.1.3 Patient-reported anti-diarrhoeal medication

Patient-reported anti-diarrhoeal medication data will be listed and summarised descriptively at each time point in each cohort. The summary will include the number and proportion of patients reporting any medication for diarrhoea during the past week. Among patients reporting anti-diarrhoea medication, the number and proportion of patients reporting different levels of helpfulness will also be summarised.

4.13.1.4 PGI-TT

PGI-TT will be summarised descriptively at each time point in each cohort. The summary will include the number and proportion of patients reporting different levels of overall side effects burden as measured by PGI-TT.

4.14 Determination of Sample Size- Module 1

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

CCI [redacted]

Cohort 1C (MCL)

CCI [redacted]

4.15 Changes in the Conduct of the Study or Planned Analysis

Not Applicable to this study.

5 REFERENCES

1. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32(27):3059-67
2. Frewer P, Mitchell P, Watkins C, Matcham J. Decision-making in early clinical drug development. Pharm Stat 2016;15(3):255-63.
3. SAS Institute Inc. 2013. SAS® 9.4 Statements: Reference. Cary, NC: SAS Institute Inc.
4. The SAS System Requirements for SAS® 9.4 Foundation for Microsoft Windows: Copyright ©2020. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
5. Hematol 2020 Jul;99(7):1595-1604. doi: 10.1007/s00277-020-04025-2. Epub 2020 May 16

6 APPENDICES

Appendix A Time windows for Module 1

Visit	**Window**	
	Physical examination | Vital signs | ECOG | Haematology | Clinical chemistry	**12-lead ECG**
Cycle 1 Day 1	1	1
Cycle 1 Day 8	2 – 11	
Cycle 1 Day 15	12 – 18	
Cycle 1 Day 22	19 – 25	
Cycle 2 Day 1	26 – 36	2-43
Cycle 2 Day 15	37 – 50	
Cycle 3 Day 1	51 – 71	44-98
Cycle 4 Day 1	72 – 99	
Cycle 5 Day 1	100– 127	

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