Title: A Modular Phase I/II, Open-label, Dose Escalation and Expansion, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of AZD0466 as Monotherapy or in Combination with Anticancer Agents in Patients with Advanced Non-Hodgkin Lymphoma

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AESI	Adverse event of special interest
Bcl-2	B-cell lymphoma 2
Bcl-xL	B-cell lymphoma-extra large
BMI	Body mass index
B-NHL	B-cell non-Hodgkin lymphoma
CI	confidence interval
eCRF	electronic case report form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
COVID-19	Coronavirus disease 2019
CR	Complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DCO	Data cut-off
DILI	Drug-induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DoR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
Gmean	Geometric mean
ICF	Informed consent form
IP	Investigational Product
IPD	Important Protocol Deviation
ITT	Intent-to-Treat
LVEF	Left ventricular ejection fraction
MCL	Mantle cell lymphoma

Abbreviation or Specialized Term	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTPI-2	Modified toxicity probability interval
MUGA	Multigated acquisition scan
MZL	Marginal zone lymphoma
NA	Not applicable
NC	Not calculable
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NQ	Non-quantifiable
NTLs	Non-target lesions
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
RP2D	Recommended Phase II dose
R/R	Relapsed/refractory
QTcF	QTc corrected by Fridericia's formula
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Stable disease
SRC	Safety Review Committee
Std Dev	Standard deviation
TEAE	Treatment emergent adverse event
TLs	Target lessions
TLS	Tumour lysis syndrome
TTR	Time to response

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	Click or tap to enter a date.	Initial approved SAP	N/A	N/A

1 INTRODUCTION

This is a modular Phase I/II, open-label, dose escalation and expansion, multicentre study that evaluates the safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of AZD0466 as monotherapy or in combination with other anticancer agents in patients with advanced non-Hodgkin lymphoma (NHL).

This SAP provides a technical elaboration of the statistical analyses for all modules as outlined in the clinical study protocol. The SAP would be amended in future modules based on the module-specific protocol amendments to include AZD0466 in combination with other anticancer treatments.

This SAP should not be read in isolation but in conjunction with the clinical study protocol (CSP) and the case report form (CRF). The analyses described in this SAP are based upon the following study documents:

- CSP, Version 2.0 (Nov 01, 2021)
- Electronic Case Report Form (eCRF), version 1.0 (Jan 26, 2022)

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

2 STUDY OBJECTIVES - CORE

The objectives and endpoints for the core protocol are provided in Table 1 below. Refer to the relevant individual modules for additional objectives and endpoints when applicable.

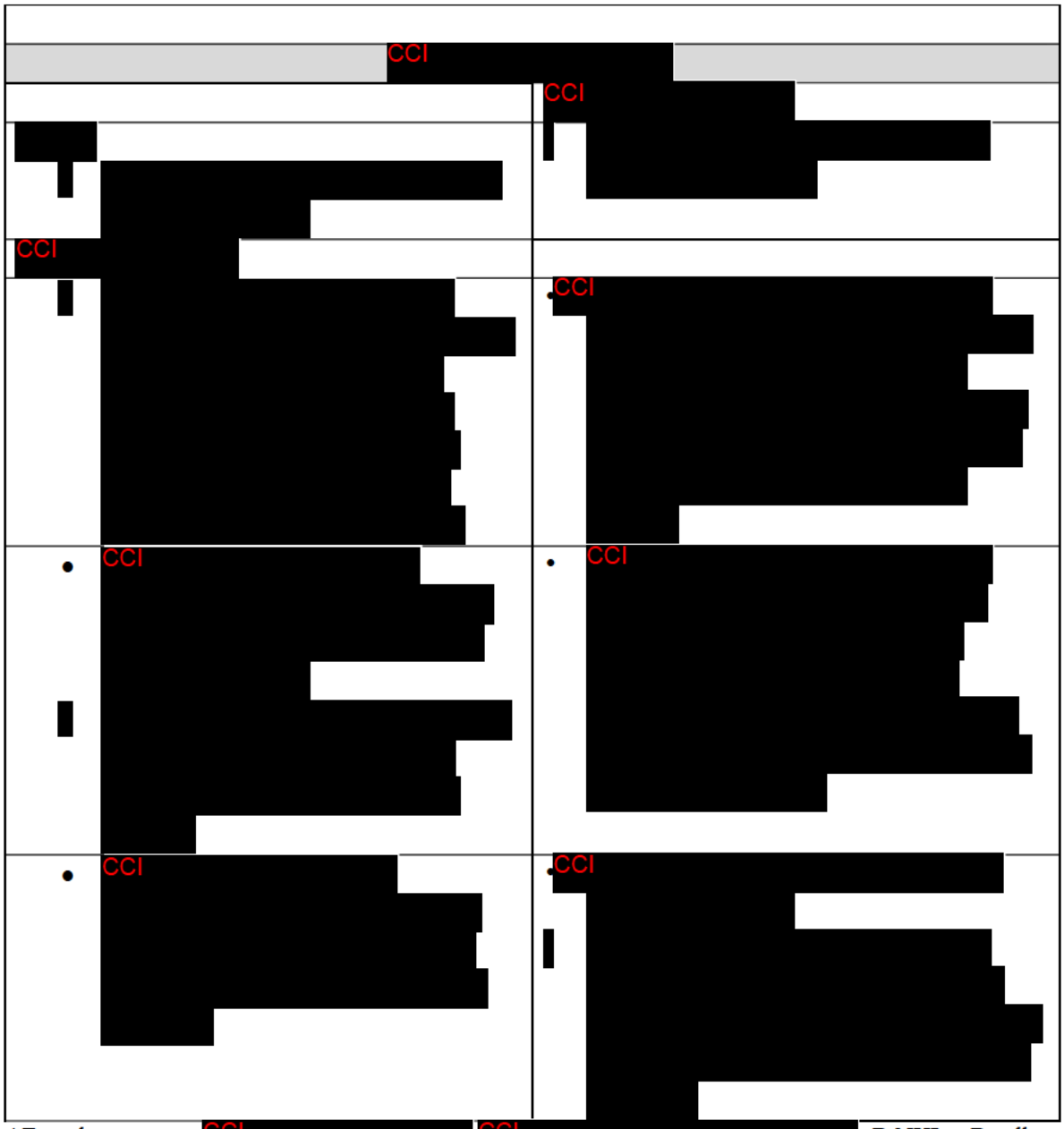
2.1 Objectives

Table 1 Objectives and Endpoints-Core

Primary Objective	
	Endpoints/Variables
Part A • To assess the safety and tolerability and identify the MTD and/or RP2D of AZD0466 as monotherapy or in combination with anticancer agents in patients with R/R B-NHL	• Incidence of AEs and DLTs • Changes from baseline in laboratory parameters, electrocardiograms, and vital signs
Part B • To assess the preliminary efficacy of AZD0466 as monotherapy or in combination with other anticancer agents in patients with R/R B-NHL	• ORR ORR is based on the revised response criteria for malignant lymphoma (Cheson et al 2014)
Secondary Objective	
	Endpoints/Variables
Part B • To assess the safety and tolerability of AZD0466 as monotherapy or in combination with anticancer agents in patients with R/R B-NHL	• Incidence of AEs and SAEs • Changes from baseline in laboratory parameters, physical examinations, performance status, electrocardiograms, and vital signs

• To assess the efficacy of AZD0466 as monotherapy or in combination with anticancer agents by evaluation of tumour response and OS in patients with R/R B-NHL	• Tumour response:
	  ○ CR rate
	  ○ DoR
	  ○ TTR
	  ○ PFS
	• OS
	Tumour response endpoints based on revised response criteria for malignant lymphoma (Cheson et al 2014)

Part A and Part B • To characterise the PK profile of study drug(s)	• Plasma concentrations and derived PK parameters for study drug(s), to be specified for each module



AE = adverse event; CCI [redacted] CCI [redacted]; B-NHL = B-cell non-Hodgkin lymphoma; CR = complete response; DLT = dose-limiting toxicity; DoR = duration of response; CCI [redacted]; MTD = maximum tolerated dose; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); RP2D = recommended Phase II dose; R/R = relapsed/ refractory; SAE = serious adverse event; TTR = time to response.

3 CHANGES TO PROTOCOL PLANNED ANALYSES - CORE

Not Applicable.

4 DATA ANALYSIS CONSIDERATION - CORE

4.1 Timing of Analyses

For the timing of analyses, refer to the individual modules.

4.2 Analysis Populations

For the definitions of the analysis population refer to the individual modules.

4.3 General Considerations

4.3.1 Data Quality Assurance

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

4.3.2 General Presentation Considerations

No formal hypothesis testing is planned for this study.

Unless stated otherwise, each module and cohort will be analysed separately.

The below mentioned general principles will be followed throughout the study:

- Continuous endpoints are summarised by the number of observations, mean, standard deviation (Std Dev), median, upper and lower quartiles (as applicable), minimum, and maximum. For data that requires log-transformation, it is more appropriate to present geometric mean, coefficient of variation (CV), median, minimum and maximum. Categorical endpoints are summarised by frequency counts and percentages for each category.

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

- Unless otherwise stated, percentages will be calculated out of the analysis set total, by dose level/cohort as appropriate.

- For continuous data, descriptive summary statistics (mean, median, Std Dev, standard error, confidence intervals [CIs]) will be rounded to 1 additional decimal place compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.

- For categorical data, percentages will be presented to 1 decimal place.
- All CIs presented will be two-sided at the 95% level unless stated otherwise.
- SAS® version 9.4 *(as a minimum)* will be used for all analyses.

4.3.3 General Study Level Definitions

Baseline is the last non-missing value obtained prior to the first dose/administration of any study treatment and any information collected after first dose/administration of study treatment is regarded as post-baseline information. If two visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose/administration with no washout or other treatment 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 is 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 is calculated in relation to date of first treatment. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, serves as sufficient evidence that the assessment occurred prior to first dose. Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured is considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose. If no value exists before the first dose/administration, then the baseline value is treated as missing.

Change from baseline will be calculated as the post-dose value minus the baseline value as:

post-baseline value - baseline value

Percent change from baseline will be calculated as:

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

Study day 1 is defined as the date of first dose of study treatment (Cycle 1 Day 1). For visits (or events) prior to first dose, study day is defined as (date of visit [event] – date of first dose of study treatment). 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 listings (such as for adverse events [AEs]) that include the derivation of "days since last dose" is defined as (event date – date of last dose) where "date of last dose" is defined as date of the most recent dosing immediately preceding the event occurrence. Thus, events

on the same day as the last dose will be described as occurring zero days from last dose of study treatment.

4.3.4 Visit Window

Visit windows will be defined for any presentations that summarize values by visit. The following conventions will apply:

- Visit windows will be exhaustive so that data recorded at any timepoint has the potential to be summarized. Inclusion within the visit window will be based on the actual date and not the intended date of the visit.

- 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 2 visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between 2 consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day.
  - Examples applicable to each module will be defined separately for that module.

- Visit windowing will be conducted up to and including the end of treatment visit. That is, the end of treatment visit will be reassigned a scheduled visit based on the study day the end of treatment visit occurred at.

- If there are more than one value per patient within a time window then the closest value to the scheduled visit date are summarised, or the earlier, in the event the values are equidistant from the nominal visit date. The listings highlight the value for the patient that contributed to the summary table, wherever feasible. Note: in summaries of extreme values, all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date.
- For summaries at a patient level, all values are included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum.
- Visit 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 visit will be assigned to the nominal visit at which that assessment was recorded, and no windowing will be performed.

- For summaries showing the maximum or minimum values, the maximum/minimum values recorded while on study treatment will be used (regardless of where it falls in an interval).

- Listings should display all values contributing to a timepoint for a patient.

- If multiple measurements are taken on the same day, a measurement due to inappropriate procedures or any other issues with the first measurement, the reassessment measurement on that day will take preference for analysis, should the values for that day be in the analysis after visit windowing rules have been applied.

4.3.5 Handling of Unscheduled Visits

All unscheduled visit data have the potential to be included in the summaries, based on the assignment of visit using visit windowing as described in Section 4.3.4. Unscheduled visits will be considered for summaries showing the maximum or minimum values recorded while on study treatment.

4.3.6 Multiplicity/Multiple Comparisons

Not Applicable.

4.3.7 Handling of Protocol Deviations in Study Analysis

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

The following general deviation categories will be defined. These deviations will be reviewed and assessed on a case-by-case basis by AstraZeneca to determine importance. Deviations considered to be important will be listed and discussed in the clinical study report (CSR) as appropriate. All decisions on importance will be made ahead of database lock and will be documented prior to the analysis being performed.

- Patients who deviate from entry criteria per CSP (Deviation 1)
- No baseline Lugano assessments on or before the date of first dose (Deviation 2)
- Received prohibited concomitant medications or therapies (Deviation 3)
- Patients deviating from prescribed dosing regimen (Deviation 4)
- Missed visits, assessments, or treatments that, in the opinion of the investigator, were due to Corona virus disease 2019 (COVID-19) global pandemic, and where there was a significant effect on either completeness, accuracy and/or reliability of the patient's data, or the patient's rights, safety or wellbeing (Deviation 5)
- Deviation from Good Clinical Practice as determined by medical review (Deviation 6)

None of the deviations should lead to subjects being excluded from any analysis populations described in the SAP, unless otherwise specified. However, if a deviation is serious enough to have a potential impact on the primary analysis, sensitivity analyses may be performed. The need for such a sensitivity analysis will be determined following review

of the protocol deviations ahead of database lock and will be documented prior to the analysis being conducted.

A list of all protocol deviations will be reviewed and decisions regarding how to handle these deviations in the analyses will be documented by the study team physician, clinical pharmacology scientist and statistician prior to database lock.

4.3.8 Missing Dates

Generally, the imputation of dates is used to decide if an observation is treatment emergent for adverse events or concomitant medications. The imputed dates should not be used to calculate durations, where the results would be less accurate.

The following are the guidelines used when partial dates are detected in the study:

- For missing diagnostic dates (e.g., disease diagnosis), if the day and/or month are missing use 01 and/or Jan. If year is missing, put the complete date to missing
- For missing AE or concomitant medication start dates the following will be applied:
  a. Missing day: Impute the 1st day of the month unless month is the same as month of first dose of study treatment then impute first dose date.
  b. Missing day and month: Impute 1st January unless year is the same as first dose date then impute first dose date.
  c. Completely missing: Impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.
  d. Imputed start date should be no later than the end date.
- For missing AE or medication end dates, the following will be applied:
  a. 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 date then impute the last dose date or the primary analysis data cut-off date.
  b. Missing day and month - impute 31st December unless the year is the same as the last dose date or the primary analysis data cut-off date then impute the last dose date or the primary analysis data cut-off date.
  c. Completely Missing – need to look at whether the AE/medication is still ongoing before imputing a date 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.
- Flags will be retained in the datasets indicating where any programmatic imputation has been applied, and in such cases, any durations would not be calculated.

- If a patient is known to have died where only a partial death date is available then the date of death is 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 and applying the following:-
  - For Missing day only – using the 1st of the month.
  - For Missing day and Month – using the 1st of January.

4.3.9 Sample Size

Refer to the individual modules for details of sample sizes.

5 STATISTICAL ANALYSIS - CORE

This section provides information on definitions, derivation and analysis/data presentation per domain.

The analyses in this section focus on items that are applicable to all modules and the module specific analyses are described separately within the individual module sections.

5.1 Study Population

The domain study population covers patient disposition, analysis sets, protocol deviations, demographics, baseline characteristics medical history, prior and concomitant medication and study drug compliance.

5.1.1 Patient Disposition and Completion Status

5.1.1.1 Definitions and Derivations

A clear account of the disposition of all patients who enter the study will be provided.

Study patient (i.e., a patient is “enrolled”) is defined as having a signed informed consent available.

The end of study and end of module is defined in protocol Section 4.4

5.1.1.2 Presentation

Patient disposition including screen failures and reason for screen failure will be summarised and listed based on all patients enrolled/screened (i.e. informed consent received) by dose level/cohort or all patients combined as defined by the current relevant tables, figures, listings (TFL) standards. The number and percentage of patients for the following are summarised:

- Patients screened
- Patients assigned to treatment
- Patients who received study treatment and patients who did not receive treatment
- Patients who discontinued treatment

- Patients ongoing in the study at data cut-off (DCO)
- Patients ongoing treatment at DCO
- Patients who terminated study.

In addition, the number and percentage of patients who discontinued treatment and who discontinued the study, including a breakdown of the reason for discontinuation will be presented for all patients.

Discontinuation of treatment and/or withdrawal from study due to COVID-19 will be presented separately.

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

The number and percentage of patients with confirmed or suspected COVID-19 infection will be presented separately, including details on COVID-19 related interruptions impacting on visits and investigational product administration. Listings of patients affected by the COVID-19 pandemic will be presented detailing any affect and impact on the study. Issues reported in the Clinical Trial Management System will be considered for presented in listings as well.

5.1.2 Analysis Sets

5.1.2.1 Definitions and Derivations

For the definitions of the analysis sets refer to the individual modules.

5.1.2.2 Presentation

The analysis sets will be summarised by dose level/cohort and for all patients combined. For the safety analyses, participants will be reported by the actual treatment(s) received and grouped by their assigned target dose level of AZD0466.

Any exclusions from analysis sets will be listed together with the reasons.

5.1.3 Protocol Deviations

5.1.3.1 Definitions and Derivations

Refer to Section 4.3.7

5.1.3.2 Presentation

The incidence of important protocol deviations (IPDs) will be summarised for the ITT analysis set by deviation categories. The number and percentage of patients in the following categories will be summarised:

- Number of patients with at least 1 IPD
- Number of patients with at least 1 pandemic related IPD
- Number of patients with at least 1 IPD, excluding pandemic related IPDs.

A listing is provided with the IPD details.

5.1.4 Demographics

5.1.4.1 Definitions and Derivations

Age is grouped accordingly in the following categories: <50, ≥ 50 - < 65, ≥ 65 - < 75 and ≥ 75 years. Each race category counts patients who selected only that category.

5.1.4.2 Presentation

Demographic will be summarised and listed for all patients in the safety analysis set (SAF) by dose level/cohort and for all particpants combined as defined by the current relevant TFL standards. The following will be summarised: age, age group, sex, race, and ethnicity.

Demographics will further be summarized separately for all patients who had confirmed or suspected COVID-19 infection. If less than 5 patients have confirmed or suspected COVID-19 infection, this will be presented in a listing rather than being summarised.

5.1.5 Baseline Characteristics

5.1.5.1 Definitions and Derivations

Body mass index (BMI) will be derived as: BMI $({}^{kg}/_{m^2}) = \frac{weight\ (kg)}{[height\ (m)]^2}$

5.1.5.2 Presentation

Patient characteristics at baseline (height, weight and BMI) will be summarized for all patients in the SAF. Baseline characteristics are listed and summarised for the FAS by dose level/cohort and for all patients combined as defined by the current relevant TFL standards. The following are summarised: height, weight and BMI.

Patient characteristics will further be summarised separately for all patients who had confirmed or suspected COVID-19 infection. If less than 5 patients have confirmed or suspected COVID-19 infection, this will be presented in a listing rather than being summarised.

5.1.6 Disease Characteristics

5.1.6.1 Presentation

Disease characteristics at baseline will be summarised and listed for all patients in the SAF by dose level/cohort and for all patients combined as defined by the current relevant TFL standards.

Summaries will be produced that present:

- NHL type
- B-symptoms
- Ann Arbor Staging

- Brain involvement
- Spleen involvement
- Bone marrow involvement
- Liver involvement
- Gastrointestinal involvement
- Extranodal involvement
- Bulky nodal disease
- FLIPI and FLIPI-2 score
- International Prognosis Index score
- Simplified MIPI
- Overexpresion of cyclin D1
- Chromosome translocation t(11;14)(q13;q32)
- EBV specification
- TP53 mutation
- ALK gene mutation positive
- MYC rearrangement by FISH
- MYC overexpression by immunohistochemistry (IHC)
- CCI rearrangement by FISH
- CCI overexpression by IHC
- CCI overexpresion by IHC
- CCI overexpresion by FISH

In addition, summaries will be produced that present summary statistics on patients' target lesions (TLs) and non-target lesions (NTLs), sum of target lesions, number of metastatic sites, other.

5.1.7 Medical History and Concomitant Disease

5.1.7.1 Definitions and Derivations

Medical history and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

5.1.7.2 Presentation

Medical history, surgical history and concomitant disease will be listed and summarised for the SAF by dose level/cohort and for all patients combined as defined by the current TFL standards.

A separate summary will be presented for patients who had confirmed or suspected COVID-19 infection. If less than 5 patients have confirmed or suspected COVID-19 infection, this will be presented in a listing rather than being summarised.

Previous Disease-related Treatment Modalities

Summaries of the number and percentage of patients who have had previous disease-related treatments will be presented for each type of modality (immunotherapy, cytotoxic chemotherapy, platinum chemotherapy, biologic therapy, experimental therapy, autologous haematopoietic stem cell transplantation, antibody-drug conjugate therapy, allogeneic haematopoietic stem cell transplantation, CAR-T cell therapy and other).

Summaries for the number and percentage of patients who had a certain number of prior regimens and the best response on most recent regimen will be produced.

All summaries on previous disease related treatment modalities will be presented for the SAF by dose level/cohort and for all patients combined.

Prior Anticancer Treatment

The number and percentage of patients who have had prior anticancer treatments will be summarised for the SAF by dose level/cohort and for all patients combined.

5.1.8 Prior and Concomitant Medications

5.1.8.1 Definitions and Derivations

For the purpose of inclusion in prior and/or concomitant medication or therapy summaries, incomplete medication or radiotherapy start and stop dates will be imputed as detailed in section 4.3.8.

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 the first dose of study treatment.
- Concomitant medications are those with a stop date on or after the first dose date of study treatment, and must have started prior to or during treatment so there is at least one day in common with the study treatment.
- Post-treatment medications are those with a start date after the last dose date of study treatment.

Disallowed medications will be identified through medical review prior to any analysis of concomitant medications.

5.1.8.2 Presentation

The number and percentage of patients who took prior and concomitant medications will be summarised by Anatomical Therapeutic Chemical (ATC) classification codes and the

generic term coded by World health organization (WHO) – Drug dictionary for the SAF by dose level/cohort and for all patients combined.

Summary of disallowed concomitant medications will be produced. All prior, concomitant and post study treatment medication data will be listed.

Missing coding terms will be listed and summarised as "Not coded".

5.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses. See Table 1 for details.

Efficacy analyses, except for OS, will be based on investigator assessments based on Lugano criteria for malignant lymphoma (Cheson et al 2014)

All efficacy results will also be listed.

All efficacy analyses will be presented by dose level/cohort.

5.2.1 Primary Endpoint – Objective Response Rate

Part B

The primary efficacy endpoint is the objective response rate (ORR) based on the Lugano classification for Non-Hodgkin Lymphoma (NHL) (Cheson et al 2014).

5.2.1.1 Definition and Derivations

The Objective Response Rate (ORR) is defined as the proportion of patients who achieve either a partial response (PR) or complete response (CR) as determined by the investigator at local site per Lugano criteria prior to any evidence of progression and will be based on the evaluable for response analysis set. A response does not need to be confirmed to be included in the calculation of ORR.

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 treatment without a response or progression, receive a subsequent anticancer 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 investigator assessment using all scans, regardless of whether the scan was scheduled or not.

Best objective response (BoR)

If data permits, this endpoint will also be considered for Part A as exploratory.

Best objective response is calculated based on overall visit responses from Lugano assessments by the investigator recorded in the eCRF. It is the best response a patient has had following start of treatment, but prior to starting any subsequent cancer 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 criteria (CR, PR, Stable disease [SD], Progressive disease (PD), and Not evaluable [NE]).

5.2.1.2 Primary Analysis of Primary Endpoint: ORR

Summaries will be produced that present the number and percentage of patients with a tumour response (CR/PR) based on the evaluable for response analysis set. ORR will be calculated and a binomial exact two-sided confidence interval at 80% and 95% using the Clopper-Pearson method will be presented for patients in the evaluable for response analysis set. Patients that have missing overall response assessments at all visits are considered as non-responders, and are therefore counted in the denominator of ORR.

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.

5.2.1.3 Sensitivity Analysis of ORR Endpoint

A sensitivity analysis will be performed on the ORR endpoint as in section 5.2.1.2 but with the intent-to-treat analysis set.

5.2.2 Secondary Endpoint: Complete Response

Part B

The Complete Response is a secondary endpoint.

5.2.2.1 Definition and Derivations

CR rate is defined as the proportion of patients who achieve CR, according to the response criteria for malignant lymphoma reported by the investigator.

5.2.2.2 Primary Analysis of Secondary Endpoint: CR

The CR rate will be calculated and binomial exact two-sided confidence intervals at 80% and 95% will be presented for patients in the evaluable for response analysis set.

5.2.3 Secondary Endpoint: Duration of Response

Part B

The Duration of Response (DoR) is a secondary endpoint.

5.2.3.1 Definition

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

5.2.3.2 Derivations

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 is defined as the latest of the dates contributing towards the first visit response of 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 are evaluated for DoR.

5.2.3.3 Primary Analysis of Secondary Endpoint: DoR

Only patients who achieved objective response (CR or PR) will be included in the summaries of DoR. Kaplan-Meier plots of DoR will be presented. The median DoR and two-sided 95% CI will be estimated using the Kaplan-Meier method. In addition, the proportion of patients still responding at 3, 6, and 12 months after initial response will also be presented. This will be based on patients in the evaluable for response analysis set.

Swimmer plots by patient (including non-responders) that clearly show the profile of each patient will be produced.

5.2.4 Secondary Endpoint: Time to Objective Response

Part B

The Time to objective Response (TTR) is a secondary efficacy endpoint.

5.2.4.1 Definition

TTR is defined as the time from first dose until the first documentation objective response.

5.2.4.2 Derivations

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

Only patients who have achieved objective response (CR or PR) are evaluated for TTR.

5.2.4.3 Primary Analysis of Secondary Endpoint: TTR

The median TTR and two-sided 95% CI is assessed using the Kaplan-Meier method (without censoring because all patients have events). The number of patients with response at different disease assessment timepoints may be provided. This is based patients in the evaluable for response analysis set.

5.2.5 Secondary Endpoint: Progression-free Survival (PFS)

Part B

The Progression Free Survival (PFS) is a secondary endpoint.

5.2.5.1 Definition

PFS is defined as the time from first dose until the date of first documented disease progression, per Lugano classification as assessed by the investigator at local site, or death (by any cause in the absence of disease progression), regardless of whether the patient withdraws from therapy or receives another anticancer prior to Lugano progression.

5.2.5.2 Derivations

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

Patients who have not progressed or died at the time of analysis, or have unknown status, are censored at the time of the latest date of assessment from their last evaluable disease assessment. However, if the patient progresses or dies immediately after two or more consecutive missed visits, the patient is censored at the time of the latest evaluable disease assessment prior to the two missed visits. Note: a NE visit is not considered as a missed visit.

Given the schedule visit assessment scheme (i.e., eight-weekly for the first 24 weeks then twelve-weekly thereafter) the definition of 2 missed visits will change.

If the previous assessment is less than study day 113 (i.e., week 16) then 2 missing visits will equate to 18 weeks since the previous assessment, allowing for early and late visits (i.e., 2 x 8 weeks + 1 week for an early assessment + 1 week for a late assessment= 18 weeks).

If the 2 missed visits occur over the period when the scheduled frequency of assessment changes from eight-weekly to twelve-weekly this will equate to 22 weeks (i.e., take the average of 8 and 12 weeks which gives 10 weeks and then apply the same rationale, hence 2 x 10 weeks + 1 week for early assessment + 1 week for late assessment =22 weeks). The time period for the previous assessment is from study days 113 to 168 (i.e., week 16 to week 24).

From week 24 onwards (when the scheduling changes to 12-weekly assessments), two missing visits equates to 26 weeks (i.e. 2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment = 26 weeks).

If the patient has no evaluable disease assessments post-baseline or does not have baseline tumour assessment data, they will be censored at Day 1 unless they die within two visits of

baseline (16 weeks plus 1 week allowing for a late assessment within the visit window) when the death date qualifies as a PFS event.

A summary of censoring rules and the date of PD/death or censoring are given in Table 2 Summary of Censoring Rules for PFS. Note that censoring overrides event in certain specified cases.

Table 2 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 tumour 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 tumour 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

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

The PFS time is always derived based on scan/assessment dates not visit dates.

Disease assessments/scans contributing towards a particular visit may be performed on different dates. The following rules are applied:

- The date of progression is determined based on the earliest of the dates of the component that triggered the progression.
- When censoring a patient for PFS the patient is censored at the latest of the dates contributing to a particular overall visit assessment.

Note: for TLs only the latest scan date is recorded out of all scans performed at that assessment for the TLs and similarly for NTLs only the latest scan date is recorded out of all scans performed at that assessment for the NTLs.

Duration of follow-up for PFS is defined as follows:

Duration of follow-up for PFS (months) = (date of PFS event (progression/death) or censoring – date of first dose + 1) / (365.25/12).

5.2.5.3 Primary Analysis of Secondary Endpoint: PFS

The analysis of PFS is based on the ITT analysis set. The number and percentage of patients experiencing a PFS event (broken down by type of event/censoring) and Kaplan-Meier plots of PFS will be presented. The median PFS and its two-sided 95% CI will be estimated using the Kaplan-Meier method (if patient numbers allow).

The treatment status at progression of patients at the time of analysis will be summarised. This includes the number (%) of patients who were on treatment at the time of progression, the number (%) of patients who discontinued study treatment prior to progression, the number (%) of patients who have not progressed and were on treatment or discontinued treatment.

A summary of the 'potential' duration of follow-up for PFS is included using median (range). This is presented for censored patients (including all types of PFS censoring).

The proportion of patients alive and progression free at every 3 months (3, 6, 9, 12, etc.) and associated two-sided 95% CI will be estimated using the Kaplan-Meier method.

5.2.5.4 Sensitivity Analysis of PFS Endpoint

A sensitivity analysis will be performed censoring PFS at the date of the last progression-free disease assessment prior to initiation of subsequent anticancer treatment.

Separately, a sensitivity analysis will also be conducted to assess the 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 on the last available tumour assessment prior to COVID-19 infection related death.

5.2.6 Secondary Endpoint: Overall Survival

The Overall Survival (OS) is a secondary efficacy endpoint.
Part B.
If data permits, this endpoint will also be considered for Part A as exploratory.

5.2.6.1 Definition

Overall survival is defined as the time from the date of first dose until death due to any cause regardless of whether the patient withdraws from study therapy or receives another anticancer therapy.

5.2.6.2 Derivations

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

Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive. Patients known to be alive or dead after the data cut-off for analysis will be censored at the DCO. Patients lost to follow-up will be censored at the date the patient is last know have been alive.

Note: Survival calls will be made in the week following the date of DCO for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the 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 possible to do so under applicable local laws.

Note: For any OS analysis performed prior to the final OS analysis, in the absence of survival calls being made, it may be necessary to use all relevant CRF fields to determine the last recorded date on which the patient was known to be alive for those patients still on treatment (since the SURVIVE module is only completed for patients off treatment if a survival sweep is not performed). The last date for each individual patient is defined as the latest among the following dates recorded on the CRFs:

- AE start, stop and change in severity dates
- Admission and discharge dates of hospitalization
- Study treatment date
- End of treatment date
- Concomitant medication start and stop dates
- Laboratory test dates
- Date of vital signs
- Disease assessment dates on CRF
- Start and stop dates of alternative anticancer treatment
- Date last known alive on survival status CRF
- End of study date

Duration of follow-up for OS is defined as follows:
Duration of follow-up for OS (months) = (date of death or censoring (date last known to be alive) – date of first dose + 1) / (365.25/12).

5.2.6.3 Handling of Dropouts and Missing Data

If a patient is known to have died where only a partial death date is available, then the date of death is 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 is treated as missing, i.e., censored at the last known alive date.

5.2.6.4 Primary Analysis of Secondary Endpoint: OS

The analysis of OS is based on the ITT analysis set. The number and percentage of patients experiencing an OS event and Kaplan-Meier plots of OS will be presented. The median OS and two-sided 95% CI will be estimated using the Kaplan-Meier method (if patient numbers allow).

Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow-up and those who have withdrawn consent will be provided.

A summary of the 'potential' duration of follow-up for OS is included using median (range). This is presented separately for censored patients.

The proportion of patients alive at every 3 months (3, 6, 9, 12, etc.) and associated two-sided 95% CI will be estimated using the Kaplan-Meier method.

5.2.6.5 Sensitivity Analysis of OS Endpoint

A sensitivity analysis will also be conducted to assess the impact of COVID-19 related deaths on OS. That is, patients who had a OS 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 on the date of their COVID-19 infection related death.

5.3 Pharmacodynamic Endpoint(s)

Refer to the individual modules.

5.4 Pharmacokinetics

For the definitions of the pharmacokinetic variables refer to the individual modules.

AZD0466 exposure is evaluated indirectly by AZD4320 concentration measurement. The term 'total' AZD4320 is defined as the sum of dendrimer-conjugated AZD4320 and released AZD4320. 'Released' AZD4320 in the plasma is the sum of protein bound and unbound AZD4320, which is not dendrimer-conjugated.

5.4.1 Pharmacokinetic Concentrations

Plasma concentrations of total and released AZD4320 and its metabolites (if available and appropriate) will be listed by actual and relative (to dose administration) sampling time. The following summary statistics will be presented for the concentrations at each time point separately by dose level and dose level/cohort:

- n below LLOQ (only for concentrations)
- Geometric Mean (gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)
- Geometric CV% (gCV, calculated as 100 √ [exp(s2)-1], where s is the standard deviation of the data on a log scale)
- Gmean + gSD (gSD calculated as exp[μ±s])
- Gmean - gSD
- Arithmetic Mean
- Arithmetic SD (SD)
- Minimum
- Median
- Maximum
- Number of observations

In listings, concentrations below the lower limit of quantification (LLOQ) will be presented as BLQ. In listings and tables where the terms BLQ or LLOQ are included, the LLOQ (numerical value) will be included in a footnote.

For the calculation of statistics, concentrations that are BLQ will be handled as follows at each time point:

- If ≤50% of the concentrations are BLQ, all BLQ values will be set to the LLOQ, and all descriptive statistics will be calculated.
- If >50%, but not all, of the concentrations are BLQ, the geometric mean, geometric CV, arithmetic mean, and arithmetic SD will be reported as 'NC' (not calculable). The maximum value will be reported from the individual data, and the minimum and median will be set as 'BLQ'.
- If all concentrations are BLQ, no descriptive statistics will be calculated. 'NA' (not applicable) will be presented for geometric CV, and arithmetic SD, and 'BLQ' will be presented for geometric mean, arithmetic mean, median, minimum, and maximum.

For PK concentration and parameter data, if there are <3 values available at a time point, only the maximum, minimum, and n will be reported; the remaining descriptive statistics will be reported as 'NC'. Concentrations that are BLQ are considered a value.

Missing samples will be reported as no sample ("NS") and excluded from analysis.

Source data shall be used in all derived PK concentrations without prior rounding

The following figures, in black and white, will be generated for total and released AZD4320, and its metabolites (if available and appropriate):

- Patient Profiles, Plasma Concentration Time Data – Linear Scale
- Patient Profiles, Plasma Concentration Time Data - Semi-Logarithmic Scale
- Gmean (± gSD), Plasma Concentration Time Data
- Gmean, Plasma Concentration Time Data - Semi-Logarithmic Scale

Individual figures will be plotted using concentration versus actual time, and mean figures will be plotted using concentration versus nominal time, by treatment or dose level and cycle/PK day, as needed. Scatter plots of PK parameters versus dose, or log-dose, may also be considered to assess dose proportionality.

5.4.2 Pharmacokinetic Parameters Calculation and Summary

The pharmacokinetic (PK) parameters of the concentration data for AZD4320 and its metabolites (if applicable) will be derived using non-compartmental methods in Phoenix® WinNonlin® Version 8.1 or higher as data applicable. The PK parameters are calculated / estimated according to AstraZeneca standards

Derived PK parameters will be summarized by cycle, separately per dose level/cohort. The following summary statistics will be presented for the estimated PK parameters, as appropriate:

- Gmean (calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- gCV (calculated as 100 √ [exp(s2)-1], where s is the standard deviation of the data on a log scale)
- Gmean + gSD (gSD calculated as exp[μ±s])
- Gmean - gSD
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum
- Median
- Maximum
- Number of observations

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings for PK parameters:

- Individual PK parameters will be presented to four significant digits, with the exception of t_{max}, which will be presented to two decimal places.
- Parameters derived directly from source data (e.g. C_{max},) shall be reported with the same precision as the source data (if this is not four significant digits).
- The mean, geometric mean, median and SD values will be reported to four significant digits, all other descriptive statistics will be reported to three significant digits except for CV% which will be presented to one decimal place.

- For t_{max} the minimum and maximum will be presented to two decimals places and all other descriptive statistics will be presented to three decimal places.
- Estimates and confidence intervals in the form of percentages will be presented to two decimal places.

5.4.3 Criteria for Handling Concentrations Below the Limit of Quantification or Missing Concentrations in Pharmacokinetic Analysis

For the non-compartmental analysis (NCA) and individual plot, if a BLQ value occurs before the first measurable concentration, it will be treated as zero. Thereafter, BLQ values will be treated as missing for PK analysis, with special situations described below. The following rules apply with special situations defined below:

- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless they are considered to be a true characteristic of the profile of the drug.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
- If a pre-dose measurement for the first dose of cycle 1 is missing it will be set to zero for a single dose, or to the minimum observed concentration for a repeat dose.

5.4.4 Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in CSR.

Quantifiable pre-dose concentration values in the first dosing of cycle 1 (i.e., the first ramp-up dose) will be considered anomalous and set to missing for the PK analysis.

5.5 Immunogenicity

Refer to the individual modules.

5.6 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, ECG, B-symptoms, and tumour lysis syndrome (TLS).

Tables will be provided for the SAF, listings are provided for all patients or the SAF depending on the availability of data.

All safety analysis will be presented by dose level/cohort. The results from the ramp-up period will be presented separately.

5.6.1 Exposure

5.6.1.1 Definitions and Derivations

- Total duration of exposure is defined by the last date of actual dosing (i.e., a dose > 0 mg/L was given) in the last cycle plus 28 days (28 is by default, the number of days in a cycle or until the next scheduled dose, there 7 days during the intrapatient ramp-up and 21 days thereafter) minus the date of first treatment study treatment.

    - For patients who die whilst on study treatment or if a DCO occurs, duration of exposure (months/weeks) is defined as date of death/DCO (whichever occurs first) minus the date of first treatment plus 1 day.

- Actual treatment duration = total treatment duration, excluding dose interruptions not in accordance with the protocol, and any planned no dose periods.

- Dose intensity of study treatment is addressed by considering relative dose intensity (RDI), where RDI is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. More specifically, RDI is defined as follows:

    - RDI = 100% × d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the actual last day of dosing. D is the total dose that would be delivered, if there were no modification to dose or schedule.

- The duration of an interruption will be calculated as [date/time treatment resumed – date/time treatment stopped]. Overall duration of interruption will be calculated as the sum of all individual interruptions during the study.

Duration of dose delays will be derived for doses indicated as being delayed on the eCRF. For each individual dose, the duration for dose delay is the number of days the dose was received outside of the original planned dosing schedule. Overall duration of dose delays will be calculated as the sum of all individual dose delays during the study.

5.6.1.2 Presentation

The total and actual duration of exposure to study treatment in months will be summarised by descriptive statistics and by frequency. Dose intensity will be summarised by descriptive statistics. Exposure to investigational product (IP)(s) i.e. total amount of study drug received will be listed for all patients. Exposure swimmer plot(s) will be produced, with a line presented for each patient to display relevant exposure and disposition details.

Dosing deviations for study treatment (s) will be summarized with reasons for deviations for the following categories: reductions and interruptions. Dosing delays will be derived based

on the scheduled dosing dates using the previous dose given as reference. The number of patients with dosing delays and total dose delays will be summarised.

The number of cycles of dose received will also be summarised.

5.6.2 Adverse Events

5.6.2.1 Definitions and Derivations

The latest or current version of MedDRA will be used to code the adverse events (AEs). AEs will be graded according to the National Cancer institute Common Terminology Criteria for AEs (using the CTCAE version 5.0).

AEs are defined as treatment emergent if they onset or worsen (by investigator report of a change in intensity/severity), during the treatment emergent phase defined below. Worsening is determined by comparison with the pre-treatment severity of the AE recorded closest to the start of dosing.

When assigning AEs to the relevant phase of the study the following rules apply and any deviations must be agreed by the study team:

- Pre-treatment phase – All AEs with a start date after signing the informed consent form (ICF), prior to the first administration of IP that do not subsequently go on to worsen during the treatment emergent phase.

- Treatment emergent phase – All AEs starting or worsening (severity) following the first administration of IP for the duration of the treatment period, up to and including 30 days after the last dose of the study treatment as per the study safety follow-up period but prior to subsequent cancer therapy. AEs with missing start time which occur on the same day as first IP administration will be reported as treatment emergent. Note that the treatment emergent phase includes the on treatment and safety follow-up periods.

- Off-treatment phase – All AEs starting more than 30 days after last dose of study treatment or once subsequent cancer therapy is started, whichever is earlier.

Serious Adverse Events (SAEs)

A serious adverse event (SAE) is an AE 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 in offspring of the patient
- Is an important medical event that may jeopardise the patient

AEs of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the IP and may require close monitoring and rapid communication by the investigator to the sponsor.

The following events will be considered to be AESIs:

- Tumour lysis syndrome
- Hepatoxicity, including potential Hy's Law, Drug-induced liver injury, Bilirubin increases with transaminase (ALT or AST, or both ALT and AST) increase
- QRS amplitude shortening

Other categories may be added, or existing terms may be modified as necessary. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which higher-level terms and which preferred terms contribute to each AESI. Further reviews may take place prior to database lock (DBL) to ensure any further terms not already included are captured within the categories.

Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert reviews the list of AEs that were not reported as SAEs and AEs leading to discontinuation of study treatment. Based on the expert's judgement, AE of particular clinical importance may, after consultation with the Global Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the Clinical Study Report. A similar review of laboratory values, vital signs, ECGs, and other safety assessments will be performed for identification of other significant adverse events. This review takes place prior to database lock, and any AEs identified will be fully documented in meeting minutes. Further review following database lock may result in ad-hoc OAEs being identified, in this case, the other OAEs and resulting summaries will be fully documented in the CSR.

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

5.6.2.2 Presentation

All AEs reported in the treatment emergent phase will be summarised and listed. Pre-treatment AEs and off-treatment AEs will be listed.

Treatment emergent adverse events (TEAEs) will be counted once for each patient for calculating percentages of patients experiencing TEAE. In addition, if the same TEAE occurs multiple times within a particular patient, the highest severity and level of relationship observed will be reported. For tables by MedDRA system organ class (SOC) and MedDRA preferred term (PT), patients with multiple TEAEs will be counted once for each SOC/PT.

An overall summary table of the number of patients experiencing each category of adverse events will be produced. The number of patients experiencing TEAEs by MedDRA SOC and PT will be summarised and the type of incidence, severity, and relationship to IP will be summarised. Further splits by CTCAE grade, causal relationship to IP and adverse events with Grade 3-4 will also be also summarised.

Separate tables present adverse events leading to discontinuation, serious adverse events, IP-related adverse events, and other significant adverse events.

Details of any deaths will be summarised and listed for all patients. AEs leading to death will also summarised.

The following summaries for the number and percentage of patients with AEs will be created by dose level/cohort and overall as appropriate:

- All AEs in any category
- AEs by SOC and PT
- AEs by SOC, PT and maximum reported CTCAE grade
- AEs above 5% of patients by PT (percentage for the threshold may be adapted as appropriate)
- AEs assessed by investigator as possibly related to study treatment by SOC and PT
- AEs leading to hospitalisation, by SOC and PT
- AEs by PT and maximum reported intensity
- AEs by PT and relationship to study treatment
- AEs leading to discontinuation of study treatment by SOC and PT
- AEs leading to discontinuation of study treatment assessed by investigator as possibly related to study treatment by SOC and PT
- AEs assessed by investigator as possibly related to study treatment by SOC, PT and maximum reported CTCAE grade.
- AEs of CTCAE grade 3 or higher assessed by investigator as possibly related to study treatment by SOC and PT
- AEs leading to study treatment dose reduction by SOC and PT Note: For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group.

- AEs leading to study treatment interruption (infusion interruption or missed dose) by SOC and PT
- Non-serious AEs occurring in greater than 5% of patients
- SAEs by SOC and PT

SAEs

SAEs will be summarised as described above for the TEAEs.

AEs of special interest

Grouped summary tables of certain MedDRA preferred terms will be produced and may also show the individual preferred terms which constitute each AESI grouping. Groupings will be based on preferred terms provided by the medical team prior to DBL, and a listing of the preferred terms in each grouping will be provided.

Summaries of the above-mentioned grouped AE categories include number and percentage (%) of patients who have:

- At least one AESI presented by event outcome
- At least one AESI causally related to IP
- At least one AESI leading to discontinuation of study treatment.

A summary of total duration (days) of AESI will be provided for events which have an end date, and this may be supported by summaries of ongoing AESIs at death and, separately, at data cut-off.

5.6.3 Death

5.6.3.1 Presentations

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

- Related to disease under investigation only
- AE outcome = death only
- Both related to disease under investigation and with AE outcome = death
- AE with outcome = death > 30 days after last study treatment
- Other deaths

A corresponding listing will also be produced.

5.6.4 Clinical Laboratory, Blood Sample

5.6.4.1 Definitions and Derivations

Laboratory tests will be grouped according to chemistry and haematology

For chemistry and haematology parameters, laboratory abnormalities with toxicity grades according to the National Cancer Institute (NCI) CTCAE version 5.0 will be derived. Laboratory variables that will be measured are detailed in Table 3.

Table 3 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)		**Clinical Chemistry (serum or plasma)**	
Haemoglobin (Hb)		Creatinine	Chloride
Leukocyte count (WBC count)		Bilirubin, total	Cortisol [a]
Leukocyte differential count		Alkaline phosphatase	TSH [a]
Neutrophils		AST	Bicarbonate
Lymphocytes		ALT	BUN/urea nitrogen
Eosinophils		Amylase [b]	Lipase [b]
Platelet count		Albumin	LDH
Urinalysis		Potassium	Phosphate
Hb/erythrocytes/blood		Calcium, total	Uric acid
pH	Ketones	Sodium	Troponin I [a]
Protein/albumin	Bilirubin	BNP (or NTproBNP) [a]	
Glucose		Magnesium	Glucose
Microscopy (red and white blood cells, bacteria, casts, and crystals) only if urinalysis is abnormal		Total protein	ACTH [a]
Coagulation		Cholesterol	GGT
International normalised ratio (INR)		Triglycerides	Ferritin
Activated partial thromboplastin time (aPPT)		High-density lipoprotein (HDL)	Creatine kinase (CK)
Prothrombin time (PT)		Low-density lipoprotein (LDL)	
Fibrinogen		**Pregnancy test (females of childbearing potential only)**	
Viral Serology		Urine human chorionic gonadotropin (hCG)	Serum beta hCG
Hepatitis B and C	CMV	**Others**	
SARS-CoV-2		Serum immunoglobulins [a]	Beta-2 microglobulin [a]

[a] At screening, at target dose (pre dose timepoint) and then as clinically indicated and at end of treatment visit.
[b] Collected at screening, pre-infusion on each dosing day, and end of treatment visit.
Lipids: triglycerides, high density lipoprotein, low density lipoprotein, and cholesterol.
ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CMV = cytomegalovirus; GGT = gamma-glutamyltransferase; LDH = lactate dehydrogenase; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TSH = thyroid-stimulating hormone; WBC = white blood cell.

Change from baseline in haematology and clinical chemistry endpoints will be calculated for each post-dose visit. CTC grade is calculated at each visit for tests with CTC grading

defined. Maximum post-baseline CTC will be also calculated. Absolute values will be compared to the local laboratory reference range and classified as low (below range), normal (within range or on limits of range) and high (above range). All values classified as high or low will be flagged on the listings.

Liver Function Parameters

Patients with elevated post-baseline alanine aminotransferase (ALT), aspartate aminotransferase (AST) or Total Bilirubin that fall into these categories will be identified. The number and percentages of these patients will be tabulated for the following parameters in **Table 4**.

Table 4 Liver Function Parameters

Liver Function Parameters	Category
ALT	• ≥3 × – ≤5 × ULN • >5 × – ≤8 × ULN • >8 × – ≤10 × ULN • >10 × – ≤20 × ULN • >20 × ULN
AST	• ≥3 × – ≤5 × ULN • >5 × – ≤8 × ULN • >8 × – ≤10 × ULN, • >10 × – ≤20 × ULN • >20 × ULN
Total bilirubin	• ≥2 × – ≤3 × ULN • >3 × – ≤5 × ULN • >5 × ULN
ALT or AST	• ≥3 × – ≤5 × ULN • >5 × – ≤8 × ULN • >8 × – ≤10 × ULN, • >10 × – ≤20 × ULN • >20 × ULN
Potential Hy's law	• (AST ≥ 3 × ULN or ALT ≥ 3 × ULN) and (Total Bilirubin ≥ 2×ULN)a

ULN: upper limit of normal range.
It includes all patients who have ALT or AST≥3xULN and total bilirubin (BILI) ≥2xULN, and in which the elevation in transaminases precede or coincide with (that is, on the same day as) the elevation in BILI.

5.6.4.2 Presentations

For all continuous laboratory assessments the absolute values and change in each parameter from baseline to each post-baseline visit will be summarised using descriptive statistics at each time point by dose level/cohort as appropriate. Graphical presentations using box plots

of absolute values and change from baseline values for haematology and clinical chemistry parameters will also be shown.

Laboratory abnormalities occurring from the start of IP administration to the last assessment on study will be presented. Worst toxicity grade, rates of grade 3-4 toxicity, and grade shifts of 2 or more from baseline to the maximum grade will be presented. Summaries indicating hyper- and hypo- directionality of change will be produced, where appropriate. Laboratory parameters that cannot be graded via NCI Common Terminology Criteria for Adverse Events (CTCAE) will be summarised with frequencies of post-baseline laboratory values categorized as low (L), normal (N), or high (H) using laboratory normal ranges compared to baseline.

Listings will be provided for all laboratory results. Laboratory parameters will be assessed at baseline as well as throughout the study.

Also, a separate table for the changes in platelets and neutrophils will be summarised over time per dose level/cohort, as appropriate.

Liver Function Parameters

Number and percentage of particpants with elevated post-baseline ALT, AST, or Total Bilirubin will be tabulated. Individual patient data where elevated ALT or AST plus total bilirubin fall into the "Potential Hy's law" will be summarised and/or listed.

Following Safety Review Committee (SRC) review of emerging data additional laboratory safety assessment sample times may be added or removed if indicated by the emerging data. For presentation of the results this analysis plan will follow the initial time schedule for these parameters.

5.6.5 Clinical Laboratory, Urinalysis

5.6.5.1 Definitions and Derivations

Laboratory urinalysis variables that will be measured are detailed in Table 3. Laboratory parameters will be assessed at baseline as well as throughout the study.

Change from baseline in urinalysis endpoints will be calculated for each post-done visit. CTC grade will be calculated at each visit for tests with CTC grading defined. Maximum post-baseline CTC will also be calculated. Absolute values will be compared to the local laboratory reference and classified as low (below range), normal (within range or on limits of range) and high (above range). All values classified as high or low will be flagged on the listings.

5.6.5.2 Presentations

Laboratory abnormalities occurring from the start of IP administration to the last assessment on study will be presented. Worst toxicity grade, rates of grade 3-4 toxicity, and grade shifts of 2 or more from baseline to the maximum grade will be presented. Summaries indicating hyper- and hypo- directionality of change will be produced, where appropriate. Laboratory parameters that cannot be graded via NCI CTCAE will be summarised with frequencies of post-baseline laboratory values categorized as low (L), normal (N), or high (H) using laboratory normal ranges compared to baseline.

Listings will be provided for all laboratory results including urinalysis.

5.6.6 Vital Signs

5.6.6.1 Definitions and Derivations

Body temperature, blood pressure, pulse rate, oxygen saturation and body weight will be assessed.

5.6.6.2 Presentations

Vital signs will be assessed at baseline and throughout the study. Vital signs may be summarised by study visit which may include descriptive statistics for the value of the parameters and the changes from baseline.

Absolute values and change from baseline for vital signs data at each timepoint will be presented using box plots.

5.6.7 B symptoms

5.6.7.1 Presentations

Information on B symptoms (unintentional weight loss of 10% or more within the previous 6 months, Disease related intermittent fevers >38 C for ≥ 2 weeks without other evidence of infection, Drenching Sweats Especially at Night for > 1 month without evidence of infection, Worsening of B-symptoms compared to baseline, Worsening of B-symptoms compared to prior visit, commnets) will be listed for all patients and visits.

5.6.8 Tumour lysis syndrome

5.6.8.1 Definitions and Derivations

Tumour lysis syndrome (TLS) is an important identified risk for AZD0466. TLS prophylaxis is mandatory for all patients starting 3 days before the first dose of AZD0466, which should be followed in addition to institutional guidelines.

5.6.8.2 Presentations

Listing of TLS Monitoring including potassium, calcium, phosphate, uric acid, cardiac arrhythmia, seizure, grade and creatinine abnormality will be presented.

A TLS-key patient table should be provided. The listing should include: Highest CTCAE grade for TLS event, presence of laboratory TLS (present/non-present), highest Cairo Bishop (Cairo and Bishop 2004) grading for clinical TLS event (if criteria clinical TLS are met).

5.6.9 Electrocardiogram

5.6.9.1 Definitions and Derivations

Electrocardiogram (ECG) parameters (triplicate recordings) will be assessed at baseline as well as throughout the study. The average of the triplicate measures taken will be used in all calculations. ECG parameters include PR, RR, QRS, QT, QTcB, and QTcF. The QTcF is considered as the primary correction method to assess patient cardiac safety.

From these resting 12-lead ECGs values of the QT and RR intervals and the QT interval corrected for heart rate using Fridericia's correction (QTcF) will be derived using the following formula:

QTcF = $QT \Big/ \sqrt[3]{RR}$ where RR is in seconds

The values of QTcF (milliseconds) will be re-derived from the values of RR and QT during the creation of the reporting database.

The notable ECG interval values while on treatment are:

- Maximum QTcF, QTcB and QTc intervals > 450 milliseconds, > 480 milliseconds, and > 500 milliseconds.
- Maximum changes from baseline in QTcF and QTcB > 30, >60, and > 90 milliseconds.

5.6.9.2 Presentations

ECG parameters will be summarised using descriptive statistics by visit and change from baseline in ECG endpoints will be calculated for each post-dose visit. Absolute values and change from baseline for ECG data at each timepoint will be presented using boxplots.

The number and percentage of patients having notable ECG interval values on treatment will be summarised.

5.6.10 Echocardiogram (ECHO)

5.6.10.1 Definitions and Derivations

In addition to screening, an ECHO should be done within 14 days after an abnormal ECG finding (T wave inversion/flattening, significant QRS amplitude changes or symptomatic patient, etc) or as soon as possible when clinically indicated. If an ECHO cannot be taken, a multi-gated acquisition (MUGA) scan to assess left ventricular ejection fraction (LVEF)

will be done. In case of any T wave abnormality, the ECHO (or MUGA) should be repeated at the 30-day follow-up visit to address the question of recovery, during the off-treatment period.

5.6.10.2 Presentations

Absolute value, change from baseline and percentage change from baseline will be presented for LVEF.

5.6.11 Other Safety Assessments

Refer to the individual modules.

6 INTERIM ANALYSIS - CORE

Refer to the individual modules.

7 STUDY OBJECTIVES – MODULE 1

The objectives and endpoints for the module 1 are provided below.

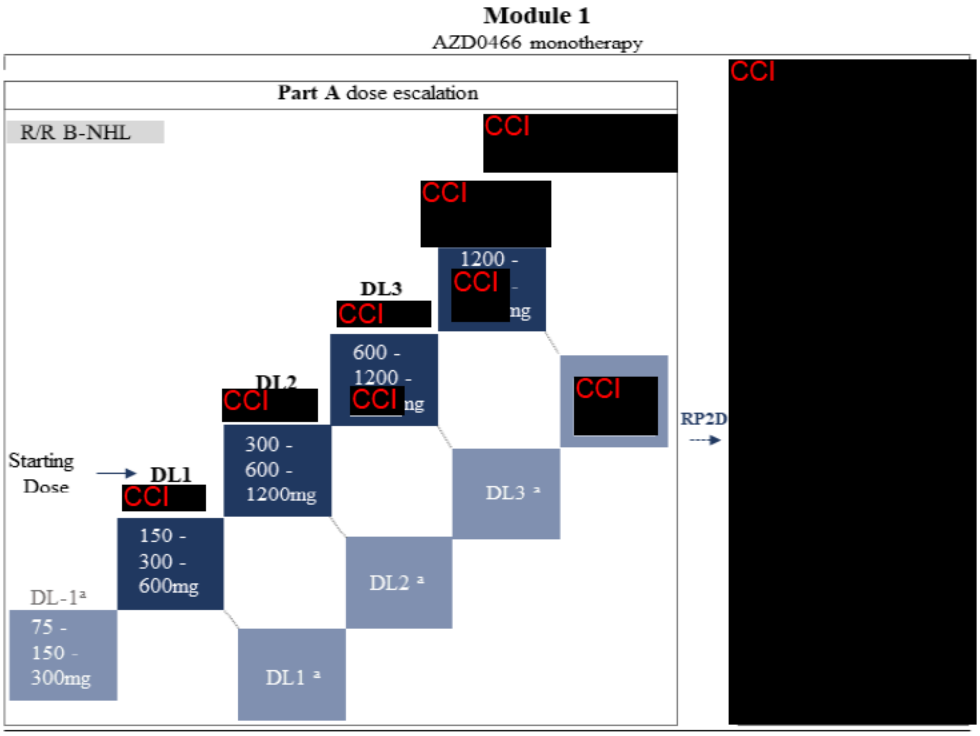
Refer to Section 2.1. Exploratory endpoints related to the pharmacodynamics, biomarkers and DNA may be reported outside of the CSR and will not be described further within this SAP.

8 STUDY DESIGN – MODULE 1

8.1 Schema

The schema for Module 1 Part A and Part B is illustrated in Figure 1.

Figure 1 Module 1 Schema



[a] Alternative dosing schedule: option of dose reduce and/or change in dosing schedule from weekly to every 2 weeks based on emerging safety data.

B-NHL = B-cell non-Hodgkin lymphoma; DL = dose level; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; MTD = maximum tolerated dose; MZL = marginal zone lymphoma; RP2D = recommended Phase II dose; R/R = relapsed/refractory.

In part A, the initial dose levels will be set according to nonclinical modelling and data from previous studies with an intra-patient dose ramp-up to mitigate the risk of TLS. The intra-patient ramp-ups will involve beginning at a specified lower dose and rapidly increase the dose to reach target value by Day 8. For example, in dose level 1, at Cycle 1 Day 1 AZD0466 will be administered at 150 mg followed by 300 mg at Cycle 1 Day 4 and reaching target dose of 600 mg at Cycle 1 Day 8. Thereafter, weekly dosing would continue at 600 mg. Each cycle is 28 days with Cycle 1 consisting of ramp-up to achieve the target dose level and then 3 doses at target level on Days 8, 15, and 22 with a 28-day DLT period (refer to Section 10.6.6.2 of the CSP for details).

8.2 Overall Design

Module 1 will evaluate the safety, tolerability, PK, and preliminary efficacy of AZD0466 as monotherapy. Module 1 comprises 2 parts: AZD0466 monotherapy dose escalation in patients with advanced B-NHL (Part A) followed by 3 independent dose expansion cohorts of patients with defined lymphoid malignancies (Part B). The Module 1 schema is illustrated in Figure 1.

- **Part A:** Phase 1 dose setting to assess the safety and tolerability and determine dose(s) and schedule(s) to be evaluated in Part B.
- **Part B:** Phase 1b/2a dose expansion to assess the preliminary efficacy of AZD0466 in 3 select patient populations: Relapsed/refractory Mantle cell lymphoma (R/R MCL) (Cohort B1) , Relapsed/refractory follicular lymphoma (R/R FL) or Relapsed/refractory Marginal zone lymphoma (RR MZL) (Cohort B2), and Relapsed/refractory diffuse large B-cell lymphoma (RR DLBCL) (Cohort B3).

An SRC will be responsible for making recommendations for dose escalation or dose de-escalation decisions after each dose level. The SRC will also assess all evaluable patients to establish the Recommended Phase II dose (RP2D) and determine if the study should progress to Part B. Refer to Appendix A 5 A5 of the CSP for details on the SRC. Further details on the decision rules for dose escalation are described with in the SRC charter.

Treatment will be administered in the outpatient setting with close monitoring. All patients will be treated until disease progression or unacceptable toxicity or withdrawal of consent. All patients should be followed for survival every 3 months after the last clinic visit until withdrawal of consent or end of study for the purpose of assessing survival status (see Section 7.1 of CSP). Patients who achieve a CR will be followed for relapse of disease until death.

9 CHANGES TO PLANNED PROTOCOL ANALYSES – MODULE 1

Not Applicable.

10 DATA ANALYSIS CONSIDERATION – MODULE 1

10.1 Timing of Analyses

The details of the analyses planned during the conduct of this study is outlined in Table 5.

Table 5 Summary of analyses During Study Conduct

Analysis	Trigger
Analysis Part A: Dose Escalation	When the MTD has been determined and the last patient to be recruited has had the opportunity to complete 2 cycles of treatment or has discontinued or withdrawn from treatment.
Interim Analysis Part B: cohort B1	Interim analysis will be performed when CCI [redacted].
Interim Analysis Part B: cohort B2	Interim analysis will be performed when CCI [redacted].
Final Analysis Expansion Cohorts (B1, B2 and B3)	Final analysis will be performed when either the last patient from all expansion cohorts has had the opportunity to CCI [redacted].

10.2 Analysis Populations

The analysis populations for Module 1 Part A and Part B are summarised in Table 6.

Table 6 Module 1 Part A and Part B Analysis Populations

Analysis population /Analysis set	Description	Endpoint/Output
Enrolled/Screened	All patients who sign the ICF	Disposition
Safety	All patients who received at least 1 dose of AZD0466. For safety analyses, participants will be reported by the actual treatment(s) received and grouped by their assigned target dose level of AZD0466	Demography Baseline Exposure Safety Performance status PK concentrations and parameters listings
Intent-to-treat	All patients who received at least 1 dose of AZD0466	OS PFS ORR
Evaluable for Response	All patients, with measurable disease at baseline, who have	ORR DoR

	received at least 2 doses of AZD0466 at the target dose level in Cycle 1	CR rate TTR
DLT Evaluable	Patients enrolled in dose escalation who have received at least 2 doses of AZD0466 at the target dose level (67% of target doses from Day 8 to Day 22 in Cycle 1) and have completed the safety follow-up through the DLT evaluation period or have experienced a DLT	DLT
Pharmacokinetics	Dosed patients with reportable plasma concentrations and no important AEs or protocol deviations that may impact PK	Plasma concentrations and derived PK parameters

DLT = dose-limiting toxicity; PK = pharmacokinetics; ICF = informed consent form; PFS = progression free survival; TTR=Time to response, OS = overall survival; DoR = duration of response; ORR = overall response rate; CR = complete response.

10.3 General Considerations

Refer to Section 4.3 of this SAP.

10.3.1 Visit Window

Refer to Section 4.3.4 of this SAP.
An example of visit windows for physical examination data up to Cycle 3 Day 1 for Module 1 are given below:

- Cycle 1 Day 8 (Study Day 8): 2-11
- Cycle 1 Day 15 (Study Day 15): 12-18
- Cycle 1 Day 22 (Study Day 22): 19-25
- Cycle 2 Day 1 (Study Day 29): 26-32
- Cycle 2 Day 8 (Study Day 36): 33-39
- Cycle 2 Day 15 (Study Day 43): 40-46
- Cycle 2 Day 22 (Study Day 50): 47-53
- Cycle 3 Day 1 (Study Day 57): 54-60

10.3.2 Handling of Unscheduled Visits

Refer to Section 4.3.4.

10.3.3 Multiplicity/Multiple Comparisons

Not Applicable.

10.3.4 Handling of Protocol Deviations in Study Analysis

Refer to Section 4.3.7.

10.3.5 Sample Size

10.3.5.1 Modified toxicity probability interval-2 (mTPI-2)

The mTPI-2 employs a simple beta-binomial Bayesian model. The posterior density of the toxicity probability is divided into multiple intervals with equal length. These intervals are categorized as underdosing (below), proper dosing (equivalent), and overdosing (above) in terms of target toxicity. The underdosing interval corresponds to a dose escalation, overdosing corresponds to a dose de-escalation, and proper dosing corresponds to staying at the current dose.

For specific dose escalation rules, refer to Section 10.6.6.1 of CSP and Section 10.3.5.2 of SAP.

10.3.5.2 Dose Escalation

Module 1 Part A (Dose Escalation): The primary objective of Part A is to identify the maximum tolerated dose (MTD) of AZD0466 monotherapy. In Module 1 Part A, a minimum of CCI patients will be enrolled in a dose cohort and evaluated through the DLT evaluation period of 28 days before a dose escalation/expansion/ de-escalation decision can be made (unless unacceptable toxicity is encountered prior to enrolment of CCI patients), while the maximum number of patients to be enrolled in any given dose cohort will be capped at CCI patients. Dose escalation (or de-escalation) will be determined by mTPI-2 with a target DLT rate of CCI% and an equivalence interval of (CCI%, CCI%). A dose level will be considered non-tolerated with no additional patients enrolled at that dose level, if it has an estimated 95% or more probability (P) of exceeding the target DLT rate of CCI [redacted] with at least CCI patients treated at that dose level. Five doses (DL-1, DL1 to DL4, start at DL1), CCI total patients, with a maximum of CCI being DLT evaluable at each dose level. The structure of the dose escalation part is shown in Figure 1.

10.3.5.3 Dose Expansion

Module 1 Part B (Dose Expansion)

Separate expansion cohorts will enrol 3 distinct populations of patients with B-cell non-Hodgkin's lymphoma: patients diagnosed with R/R MCL will be enrolled in Cohort B1, R/R FL or R/R MZL patients in Cohort B2, and R/R DLBCL patients in Cohort B3. Cohorts B1 and B2 will recruit up to CCI patients, and Cohort B3 will recruit approximately CCI patients. These sample sizes have been determined to ensure confidence intervals constructed around the complete ORR, as calculated after all patients have had the opportunity to complete 2 treatment cycles, will provide sufficient information to enable

decisions to be made around the likely success of future studies in these patient populations, using methodology described in Frewer et al 2016 (Frewer et al 2016).

CCI

Refer to Section 10.9.2 of the CSP for details of the target values for cohorts B1, B2 and B3.

11 STATISTICAL ANALYSIS – MODULE 1

This section provides information on definitions, derivation and analysis/data presentation per domain.

11.1 Study Population

11.1.1 Patient Disposition and Completion Status

Refer to Section 5.1.1 of this SAP.

11.1.2 Analysis Sets

11.1.2.1 Definitions and Derivations

Refer to Table 6 of Section 10.2 of this SAP.

11.1.3 Protocol Deviations

Refer to Section 5.1.3 of this SAP.

11.1.4 Demographics

Refer to Section 5.1.4 of this SAP.

11.1.5 Baseline Characteristics

Refer to Section 5.1.5 of this SAP.

11.1.6 Disease Characteristics

Refer to Section 5.1.6 of this SAP.

11.1.7 Medical History and Concomitant Disease

Refer to Section 5.1.7 of this SAP.

11.1.8 Prior and Concomitant Medications

Refer to Section 5.1.8 of this SAP.

11.1.9 Dose-Limiting Toxicity(DLT)

11.1.9.1 Definitions and Derivations

A DLT will be defined as the occurrence of any of the following during the 28-day DLT evaluation period in Cycle 1, unless unequivocally due to underlying malignancy or an extraneous cause. For more details including maximum tolerated dose, refer to Section 10.6.6 of the CSP.
Any event that meets the DLT criteria in the opinion of the Investigator should be reported to the study physician within 24 hours of knowledge of the event. Events will be assessed for DLT criteria according to the NCI CTCAE v5.0 except for TLS, which will be assessed for DLT criteria using the Howard et al 2011 modification of Cairo-Bishop 2004 criteria (Cairo and Bishop 2004).

Any patient who is not evaluable for DLT assessment will be replaced, with the exception of a patient who experiences a DLT; these patients will not be replaced. Additional patients enrolled at a previously cleared dose level to provide supplemental safety, efficacy, PK, and pharmacodynamics data will not be replaced or evaluated for DLT in support of dose escalation decisions. However, these additional patients will be included in the determination of the MTD/RP2D upon completion of the dose escalation part.

A DLT evaluable patient is defined as a patient enrolled in Module 1 Part A (dose escalation), who has received at least 2 doses of AZD0466 at the target dose level (67% of Cycle 1 after ramp-up) and has completed safety follow-up through the DLT evaluation period, or has experienced a DLT.

During Part A of Module 1, AZD0466 monotherapy dose escalation, AstraZeneca pharmacovigilance process and the SRC will evaluate toxicities study-wide (including evaluation of previous doses). During Part B of Module 1, AZD0466 monotherapy dose expansion, a safety analysis will be performed at the time of the first interim analysis in each cohort (Cohort B1 at CCI patients, Cohort B2 at CCI patients) and Cohort B3 at CCI patients, pooling safety data from all available patients. The study recruitment may be paused, pending investigation by the Sponsor and in discussion with SRC, if CCI % of patients experience safety events that meet the DLT criteria, see Section 10.6.6.3 of CSP (including AEs of special interest [Section 8.3.6]), the SRC, will decide to stop the study, modify the study, or continue the study, based on the overall risk benefit of the agent. Throughout the expansions, the AZ safety team and the SRC, will regularly review cumulative safety data including, but not limited to, toxicities that meet the DLT criteria.

11.1.9.2 Presentation

The number of Part A dose-setting patients evaluable for determination of DLTs during Cycle 1 and the number of patients with any DLT (and their categorization) will be summarised by dose level and based on the DLT evaluable analysis set. The MTD will be

selected from all tried dose levels that have not been previously declared to be unsafe with a DU decision according to the mTPI-2 algorithm (see CSP Table 15). With this constraint, the MTD will be determined as the dose level with the DLT estimate closest to the target toxicity level of CCI %. The MTD will be determined by isotonic regression analysis applied to Cycle 1 DLT rates observed during dose exploration using the mTPI-2 method (Ji et al 2010).

In the case of dose levels with estimated toxicity of equal distance (tied dose levels) from the target toxicity of CCI %, the following approach is used: among all tied dose levels the highest dose level with target toxicity CCI % will be selected, unless all tied dose levels have estimated toxicity CCI %, in which case the lowest dose level will be selected. Part B patients in Cycle 1 meeting the same criteria for DLT evaluability that were used for Part A dose setting, and the number/percentage of those patients with any safety events that meet the DLT criteria (and their categorization) , will be summarised for Part B RP2D-treated patients.

The number and percentage will be reported for pooled RP2D-treated Part A and Part B patients that experienced at least one safety event that meet the DLT criteria after receiving any amount of study treatment from Cycle 2 onwards. The numbers and types of toxicities that meet the DLT criteria and the cycles (weeks) in which they were observed will also be summarised.

11.2 Endpoint Analyses

Refer to Section 5.2 of this SAP.

11.4 Pharmacodynamic Endpoint(s)

The pharmacodynamic effects of AZD0466 will be assessed by evaluation of laboratory parameters which will be reported within the safety section of the CSR. Further exploration of potential biological activity by the assessment of pharmacodynamics and exploratory biomarkers will be reported outside the main CSR.

11.5 Pharmacokinetics

This section covers details related to pharmacokinetics endpoints and analyses.

11.5.1 Definitions and Derivations

Plasma PK Parameters

PK analysis will be, where data allow, carried out using actual elapsed times determined from the PK sampling and dosing times recorded in the database. If actual elapsed times are missing, nominal times may be used at the discretion of the PK scientist with approval from the AZ Clinical Pharmacology Scientist. Nominal sampling times may be used for any agreed interim PK parameter calculations.

Where data allow, the following PK parameters for total and released AZD4320 will be derived from plasma concentrations:

Plasma

C_{max}	Maximum observed plasma (peak) drug concentration
t_{max}	Time to reach peak or maximum observed concentration or response following drug administration
λz	Terminal rate constant, estimated by log-linear least squares regression of the terminal part of the concentration-time curve
$t_{1/2}$λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
AUC_{0-24}	Partial area under the plasma concentration-time curve from time 0 to 24 hours after the start of infusion
AUC_{0-72}	Partial area under the plasma concentration-time curve from time 0 to 72 hours after the start of infusion
AUC_{last}	Area under the plasma concentration-curve from time 0 to the last quantifiable concentration
t_{last}	Time of last observed (quantifiable) concentration
C_{trough}	Concentration prior to dosing
Dose normalised AUC_{last}[a]	Area under the plasma concentration-time curve from time 0 to time of last quantifiable analyte concentration divided by the dose administered
Dose normalised AUC_{0-72}[a]	Area under the plasma concentration-time curve from time 0 to 72 hours after the start of infusion
Dose normalised C_{max}[a]	Maximum observed plasma (peak) drug concentration divided by the dose administered

[a] Calculated for total AZD4320 only

The following diagnostic parameters for plasma PK analysis will be provided:

λz lower	Lower (earlier) t used for λz determination
λz upper	Upper (later) t used for λz determination
λzN	Number of data points used for λz determination
Rsq	Statistical measure of fit for the regression used for λz determination
Rsq adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (n obs)

Additional PK parameters may be calculated as appropriate.

The time period used for the estimation of apparent terminal elimination half-lives, where possible, should be over at least two half-lives. For $t_{1/2}$ estimates where λ_z was calculated over a time period less than twice their resultant half-life, the reliability of $t_{1/2}$ and any PK parameters derived from λ_z will be discussed in CSR.

11.5.2 Presentation

For the definitions of handling, calculation and presentation of pharmacokinetic concentrations and parameters refer to Section 5.4.

11.6 Immunogenicity

Not applicable.

11.7 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, and ECG.
Tables are provided for the SAF, listings are provided for All patients or the SAF depending on the availability of data.

11.7.1 Exposure

Refer to Section 5.6.1 of this SAP.

11.7.2 Adverse Events

Refer to Section 5.6.2 of this SAP.

11.7.3 Clinical Laboratory

Refer to Section 5.6.4 of this SAP.

11.7.4 Vital Signs

Refer to Section 5.6.6 of this SAP.

11.7.5 Electrocardiogram

Refer to Section 5.6.9 of this SAP.

11.7.6 Other Safety Assessments

Refer to Section 5.6.11 of this SAP.

12 INTERIM ANALYSIS – MODULE 1

12.1 Dose Escalation Committee

This study will utilise an SRC, as described below:

A study-specific SRC will review the emerging data from the study and will monitor safety data on an ongoing basis.

The SRC will consist of:

- Study Chair, who will chair the committee, or delegate
- Principal Investigator or delegate from the investigational sites that have enrolled patients
- Study Physician for the study or delegate
- Medical Science Director or delegate

In addition, one other physician from the following may be invited:

- Global Safety Physician or delegate
- Senior Physician from another project.

The Study Pharmacokineticist, Study Statistician, Patient Safety Scientist, Clinical Project Manager, and other experts may also be invited as appropriate. The SRC Charter document for this study will define the exact membership, and who should be present for decisions to be made, how reviews will be performed and how the discussions will be documented. More details are found in Appendix A5 of the CSP.

12.2 Interim Analysis

For details, see Section 10.1 of this SAP for planned analyses and the DLT criteria in Section 10.6.6.3 of the CSP.

13 REFERENCES

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14 APPENDIX

The schedule of activities for Module 1 Part A and Part B is presented in Table 7 for screening and Cycle 1 and in Table 8 for Cycle 2 and beyond and follow-up.

Table 7 Schedule of Activities for Module 1 Part A and Part B: Screening and Cycle 1

Procedure	**Screening**	**Cycle 1 (28 days)**										**Details in CSP section or appendix**
		Ramp-up				**Target dose**						
Day	**-28 to -1**	**1**	**2**	**4**	**5**	**8**	**9**	**10**	**11**	**15**	**22**	
Visit window		**± 2 days (unless indicated otherwise)**										
Informed consent	X											A 3
Inclusion and exclusion criteria	X											5.1, 5.2, 10.5.1, , 10.5.2
Demography	X											8
Medical history	X											8
Disease characteristics	X											NA
Disease prognostic scores	X											Appendix M
Physical examination	X	X	X	X	X	X				X	X	8.2.1
Height	X											8.2.1
Weight	X	X				X					X	8.2.1
Vital signs	X	X	X	X	X	X	X			X	X	8.2.2
ECOG performance status	X	X										8.2.5.2
Concomitant medication	X	X	X	X	X	X				X	X	6.5
Adverse events	X	X	X	X	X	X	X			X	X	8.3
Safety ECGs (triplicate)	X	X	X	X	X	X	X			X	X	8.2.3, 10.8.2.3

24-hour continuous 12-lead ECG (Holter) recording for PK purpose						X[a]						8.2.3, 10.8.2.3
Cardiac MUGA/MRI/ECHO	X											8.2.5.1
Fresh or archival tumour sample	X	As clinically indicated										10.8.6.3
Laboratory tests												
SARS-CoV-2 test	X											8.2.4
Pregnancy test (WOCBP)	X	X										8.2.4
Haematology	X	X		X		X				X	X	8.2.4
Clinical chemistry	X	X		X		X				X	X	8.2.4
Serum immunoglobulins	X					X						8.2.4
Beta-2 microglobulin	X					X						8.2.4
Amylase and lipase	X	X		X		X				X	X	8.2.4
Coagulation	X	X		X		X				X	X	8.2.4
Cortisol, ACTH, TSH	X					X						8.2.4
Troponin I[b]	X					X						8.2.4, 8.2.4.1
BNP (or NTproBNP)	X					X						8.2.4, 8.2.4.1
Hepatitis B and C	X	For patients with positive serology for HBV or HCV, HBV DNA or HCV RNA every 3 months										8.2.4

[a] Only applies to patients enrolled in cohorts for which the treatment dose has not been cleared by the Safety Review Committee in previous AZD0466 clinical studies. Sites will be notified which cohort(s) Holter monitoring will apply to.
[b] Troponin T may be collected using a standard assay instead of troponin I, provided the results remain within normal range; However, if an abnormal troponin T value is recorded, collection of troponin I will be required thereafter, as it is more cardiac-specific.

CMV	X											8.2.4
Urinalysis	X	X		X		X				X	X	8.2.4
Disease assessments												
CT scan	X											8.1.2
FDG-PET scan[c]	X											8.1.2
Bone marrow biopsy/aspirate	X											8.1.1
B-symptoms	X											8.2.4
Endoscopy/histology	X (as clinically indicated)											8.1.4.1
Brain MRI/CT scan	X											8.1.2
Study intervention												
Administer AZD0466		X		X		X				X	X	6.1, 6.2.1
Prophylaxis for Tumour Lysis Syndrome												
Prophylaxis for TLS		X[d] (based on risk profile)		X[d] (based on risk profile)		X[d] (based on risk profile)				X[d] (based on risk profile)	X[d] (based on risk profile)	Appendix F
Pharmacokinetic assessments												

[c] Prophylaxis for TLS (hydration and anti-hyperuricaemic agents) is required for all patients receiving study intervention and should be implemented according to the TLS risk level. Prophylaxis is not provided by the study, is not given at the same frequency as the study intervention, and varies based on risk. See Appendix F, Appendix F 1.2 for details.

[d] More than one assessment to be performed at the visit.

Blood samples for plasma PK		X[e]		X[e]		X[e]	X	X (Part A only)	X (Part A only)			10.8.5.1
Pharmacodynamic assessments												
Blood samples for locally collected PBMCs	X	X[e]	X (Part A only)			X[e]	X					10.8.5.2
Exploratory and biomarkers assessments												
CCI [redacted]		X										10.8.6.1
Blood samples for CCI [redacted]	X	X				X					X	8.1.4.2, 10.8.6.4
Blood samples for CCI [redacted]	X	X				X					X	10.8.6.5
Blood samples for CCI [redacted]	X	X				X	X					10.8.6.6
Blood samples for CCI [redacted]	X	X				X	X					10.8.6.7
Blood samples for CCI [redacted]	X	X										10.8.6.8, 10.8.6.9
Blood samples for CCI [redacted]	X	X				X					X	10.8.6.10
Pharmacogenetic sampling (optional)												

[e] MZL patients with FDG-PET non-avid lesion, only require a CT scan.

CCI [redacted]		X										8.7

[f] If for any reason the sample is not drawn at Cycle 1 Day 1, it may be taken at any visit until the last study visit.
ACTH = adrenocorticotropic hormone; BNP = brain natriuretic peptide; CCI [redacted]; CMV = cytomegalovirus; CR = complete response; CSP = clinical study protocol; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; HBV = hepatitis B virus; HCV = hepatitis C virus; MCL = mantle cell lymphoma; CCI [redacted]; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; MZL = marginal zone lymphoma; NA = not applicable; NTproBNP = N-terminal pro brain natriuretic peptide; PBMC = peripheral blood mononuclear cell; PET = positron emission tomography; PK = pharmacokinetics; R/R = relapsed/refractory; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TLS = Tumour Lysis Syndrome; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Table 8 Schedule of Activities for Module 1 Part A and Part B: Cycle 2 and Beyond and Follow-up

Procedures	**Cycle 2 (28 days)**		**Cycle 3 and beyond (28 days)**		**EoT**	**Follow-up**		**Details in CSP section or appendix**
Day	**1**	**8/15/22**	**1**	**8/15/22**		**Post-treatment FU visit (28 days after last dose)**	**Q3M after post-treatment FU visit**	
Visit window	**± 2 days**				**± 7 days**			
Physical examination	X	X	X	X	X			8.2.1
Weight	X	D15	X	D15	X			8.2.1
Vital signs	X	X	X	X	X			8.2.2
ECOG performance status	X		X		X			8.2.5.2
Concomitant medication	X	X	X	X	X	X		6.5
Adverse events	X	X	X	X	X	X		8.3
Safety ECGs (triplicate)	X	D8	Even cycles only beginning at C4		X			8.2.3, 10.8.2.3
Cardiac MUGA/MRI/ECHO		D8		D8, every 3 cycles from C5	X			8.2.5.1
Fresh tumour sample	As clinically indicated							10.8.6.3
Survival status						X	X	NA
Laboratory test								
SARS-CoV-2 test	X		X					8.2.4
Pregnancy test (WOCBP)	X		X		X			8.2.4
Haematology	X	X	X	X	X			8.2.4
Clinical chemistry	X	X	X	X	X			8.2.4
Serum immunoglobulins					X			8.2.4
Beta-2 microglobulin					X			8.2.4
Amylase and lipase	X	X	X	X	X			8.2.4

Coagulation	X	X	X	X	X			8.2.4
Cortisol, ACTH, TSH					X			8.2.4
Troponin I[a]					X			8.2.4
BNP (or NTproBNP)					X			8.2.4
Urinalysis	X	X	X	X	X			8.2.4
Disease assessments								
CT scan	Weeks 8, 16, 24, 36, 48 and thereafter every 24 weeks for R/R FL and MZL, and every 16 weeks for R/R MCL and R/R DLBCL, until disease progression							8.1.2
FDG-PET scan	Week 8, 24 and 48 and thereafter once a year. If confirmed CR, no further PET scans are required.							8.1.2
Bone marrow biopsy/aspirate	To confirm CR (if prior bone marrow involvement) or as clinically indicated							8.1.1
Endoscopy/histology	To confirm CR (if prior gastrointestinal involvement), or as clinically indicated							8.1.4.1
Brain MRI/CT scan	Only if clinically indicated							8.1.2
B-symptoms	To be collected at Screening, and every tumour assessment scan							8.1.4.3
Study intervention								
Administer AZD0466	X	X	X	X				6.1, 10.6.1
Prophylaxis for Tumour Lysis Syndrome								
Prophylaxis for TLS	X[b] (based on risk profile)	X[b] (based on risk profile)	X[b] (based on risk profile)	X[b] (based on risk profile)				Appendix F
Pharmacokinetic assessments								

[a] Troponin T may be collected using a standard assay instead of troponin I, provided the results remain within normal range; However, if an abnormal troponin T value is recorded, collection of troponin I will be required thereafter, as it is more cardiac-specific.
[b] Prophylaxis for TLS (hydration and anti-hyperuricaemic agents) is required for all patients receiving study intervention and should be implemented according to the TLS risk level. Prophylaxis is not provided by the study, is not given at the same frequency as the study intervention, and varies based on risk. See Appendix F, Appendix F 1.2 for details.

Blood samples for plasma PK	X[c]		C3D1 [c], C5D1 [c]				10.8.5.1
Exploratory and biomarkers assessments							
Blood samples for CCI	X	D15 (Part B only)	C3D1, C5D1, C7D1, C9D1 (and at every tumour assessment scan)	X			8.1.4.2, 10.8.6.4
Blood samples for CCI	X	D15 (Part B only)	C3D1, C5D1, C7D1, C9D1 (and at every tumour assessment scan)	X			10.8.6.5
Blood samples for CCI	X		C3D1, C5D1 (and at every tumour assessment scan during Part B only)	X			10.8.6.6
Blood samples for CCI	X		C3D1, C5D1 (and at every tumour assessment scan during Part B only)	X			10.8.6.7
Blood samples for CCI	X		C3D1, C5D1 (and at every tumour assessment scan)	X			10.8.6.8, 10.8.6.9
Blood samples for CCI	X	D15	C3D1, C5D1, C7D1, C9D1 (and at every tumour assessment scan)	X			10.8.6.10

[c] More than one assessment to be performed at the visit. ACTH = adrenocorticotropic hormone; C = Cycle; CCI CSP = clinical study protocol; CR = complete response; CT = computed tomography; D = Day; DLBCL = diffuse large B-cell lymphoma; FDG = fluorodeoxyglucose; FL = follicular lymphoma; BNP = brain natriuretic peptide; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = end of treatment; FU = follow-up; MCL = mantle cell lymphoma; CCI ; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; MZL = marginal zone lymphoma; NA = not applicable; NTproBNP = N-terminal pro brain natriuretic peptide; CCI ; PET = positron emission tomography; PK = pharmacokinetics; Q3M = every 3 months; R/R = relapsed/refractory; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TLS = Tumour Lysis Syndrome; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

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