**Parexel International**

AstraZeneca

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# A Modular Phase I/II, Open-Label, Multi-Centre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of AZD0466 Monotherapy or in Combination in Patients with Advanced Haematological Malignancies

## Statistical Analysis Plan

**Version:** Final 2.0

**Parexel Project Number:** 254945

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## LIST OF ABBREVIATIONS

| Abbreviation / Acronym | Definition / Expansion |
|---|---|
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALL | Acute Lymphoblastic Leukaemia |
| AML | Acute Myeloid Leukaemia |
| ATC | Anatomical therapeutic chemical |
| AUC | Area under the concentration-time curve |
| $AUC_{(0\text{-}inf)}$ | AUC from time zero extrapolated to infinity |
| $AUC_{(0\text{-}t)}$ | AUC from time zero to the last quantifiable concentration |
| BICR | Blinded independent central review |
| BID | twice daily |
| BLQ | Below the lower limit of quantification |
| BMI | Body Mass Index |
| BP | Blood pressure |
| bpm | Beats per minute |
| BUN | Blood Urea Nitrogen |
| CR | Complete response |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| $C_{max}$ | Maximum observed concentration |
| CSR | Clinical Study Report |
| CV | Coefficient of variation |
| DBP | Diastolic blood pressure |
| DCO | Data cut-off |
| DDI | Drug-drug interaction |
| DLBCL | Diffuse large B-cell lymphoma |
| DLT | Dose-limiting toxicity |
| DoR | Duration of response |
| ECG | Electrocardiogram |

| Abbreviation / Acronym | Definition / Expansion |
|---|---|
| ECHO | Echocardiogram |
| ECOG | Eastern Co-operative Oncology Group |
| eCRF | electronic Case Report Form |
| EOT | End of treatment |
| Gmean | geometric mean |
| HI | Haematological improvement |
| IP | Investigational Product |
| IPI score | International Prognosis Index score |
| IV | Intravenous |
| KM | Kaplan-Meier |
| LDH | Lactate dehydrogenase |
| LLOQ | Lower limit of quantification |
| LVEF | Left ventricular ejection fraction |
| MDS | Myelodysplastic syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic resonance imaging |
| MTD | Maximum tolerated dose |
| mTPI-2 | modified toxicity probability interval |
| MUGA | Multi-gated acquisition scan |
| NA | Not available |
| NCS | Not clinically significant |
| NK | Not known |
| ORR | Overall response rate |
| OS | Overall survival |
| PD | Pharmacodynamic |
| PET | Positron-emission tomography |
| PK | Pharmacokinetics |
| PKS | Pharmacokinetic analysis set |
| PR | Partial response / Partial remission |
| PT | Preferred term |

| Abbreviation / Acronym | Definition / Expansion |
|---|---|
| QT | The QT interval is measured from the beginning of the QRS complex to the end of the T wave |
| QTc | Corrected QT interval |
| QTcF | QT corrected using Fridericia's formula |
| RP2D | Recommended Phase II dose |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SBP | Systolic blood pressure |
| SD | Standard deviation or single dose |
| SFU | Safety follow-up |
| SoA | Schedule of Activities |
| SOC | System Organ Class |
| SRC | Safety Review Committee |
| TLS | Tumour lysis syndrome |
| TTR | Time to response |
| ULN | Upper limit of normal |
| $t_{max,ss}$ | Time corresponding to occurrence of $C_{max,ss}$ at steady state |
| $V_{ur}$ | Measured overall volume of urine collected during each collection interval |
| $V_z/F$ | Apparent volume of distribution during terminal phase |
| $V_z/F_{,ss}$ | Apparent volume of distribution during terminal phase at steady state |
| WBC | White blood cell count |
| WHODRUG | World Health Organisation Drug Dictionary |
| $\lambda_z$ | Terminal elimination rate constant |
| $\lambda_{z,ss}$ | Terminal elimination rate constant at steady state |

## AMENDMENT HISTORY

| Date | Brief description of change |
|---|---|
| 7 September 2021 | Initial version 1.0 |
| 14 December 2023 | Version 2.0 includes the following changes from V1.0:<br>• Study was prematurely terminated on 28 July 2023;<br>  • Sections and paragraphs which were dedicated to module 1 part B were removed.<br>  • Analysis descriptions were aligned to the tables, listings, figures as planned to be included into the synoptic CSR<br>• Section 3.2.1.1 Response Evaluation Criteria – AML<br>  • Divided response categories for Module 1 Part A and Part B.<br>• Section 4.6.2.1 Important Protocol Deviations<br>  • Deviation 4 rephrased.<br>• Section 4.14.1 Exposure and treatment administration<br>  • Exposure is also measured by the number of cycles received.<br>• Section 4.13.2 Pharmacokinetic Parameters Calculation and Summary<br>  • Added to summarize PK concentrations also by actual dose level<br>• Section 4.14.1 Exposure and treatment administration.<br>  • Added exposure is also measured by the number of cycles.<br>• Section 4.14.4 Adverse events<br>  • Period for AEs observed as treatment emergent after study treatment changed from 30 to 28 days,<br>  • OAEs (other significant AEs) removed.<br>• Section 4.14.8 ECGs<br>  • ECG parameters will be summarized and plotted for the average from the triplicate ECG measurements.<br>• Section 6.3 Exploratory Objective(s)<br>  • Exploratory objective added: haematological improvement in intermediate and higher risk MDS patients.<br>• Section 7.2.1.5 Minimal Residual Disease (Part B only) was removed<br>• Section 7.2.2 Pharmacokinetic Variables<br>  • Several parameters added AUCs (0-36), (0-24) added.<br>• Section 8.3.1 Data cut-off removed<br>• Section 8.10 Efficacy Evaluation<br>  • Removed parameters CR, TTR, DoR from the list of objectives<br>• Section 8.10.2.1 Complete Response (CR+CRi) Rate removed<br>• Section 8.10.2.2 Time to Response (TTR) removed<br>• Section 8.10.2.3 Duration of Response (DoR) removed |

| Date | Brief description of change |
|---|---|
| | • Sections 8.10.2.2, 8.10.2.3, 8.10.3.1 Efficacy evaluation<br>  • Disease progression revised as treatment failure and relapse, as applicable.<br>• Section 8.10.3.3 Minimal/Measurable Residual Disease (Part B Only) removed<br>• Section 8.10.3.4 added for haematological response in intermediate and higher risk MDS patients (Part A Only)<br>• Section 8.13.1.2 Part B Monotherapy Dose Expansion removed<br>• Section 8.14 Interim Analysis changed to (Not applicable)<br>• Minor editorial changes |

# 1 INTRODUCTION - Core

This is a modular, Phase I/II study of AZD0466 as monotherapy or in combination with other treatments in patients with advanced haematological malignancies. The core sections of the SAP contains information applicable to all analyses planned in this study, more specific details are provided in the sections related to the individual modules.

The sponsor made the decision to terminate the study on July 28, 2023. Recruitment was stopped on June 16, 2023 and patients were followed up until the planned LPLV date of August 8, 2023. At the time of stopping recruitment, Module 1 Part A, and Module 2 were ongoing. The decision was also made not to initiate Module 1 Part B. Therefore, this statistical analysis plan (SAP) provides the technical elaboration of the statistical analyses for Module 1 Part A, and Module 2.

The analyses described for Module 1 and 2 in this SAP are based upon the following study documents and reporting standards:

- Study Protocol, Version 4.0 (September 29, 2022)
- Electronic Case Report Form (eCRF), Version 8.0 (March 13, 2023)
- AZ Corporate CSRHLD Reporting Standards v3.3
- Oncology Guidance Version 3.0
- Early Phase Oncology Guidance Version 1.0
- AZ Guideline: Pharmacokinetic Evaluations in Clinical Studies v2.3

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

# 2 STUDY OBJECTIVES – Core

## 2.1 Primary Objective

| Objectives | Endpoints/Variables |
|---|---|
| To assess the safety and tolerability of AZD0466 in patients with advanced haematological malignancies | Incidence of AEs and SAEs<br>Changes from baseline in laboratory findings, physical examinations, performance status, electrocardiograms, and vital signs |

For further and more detailed definitions of primary study objectives refer to the individual modules.

## 2.2 Secondary Objectives

| Objectives | Endpoints/Variables |
|---|---|
| To characterise the PK profile of AZD0466 following intravenous administration (via PK profiles of the active moiety AZD4320 in plasma) | Plasma concentrations and derived PK parameters for total and released AZD4320, to be specified for each module |

For further and more detailed definitions of the secondary study objectives refer to the individual modules.

## 2.3 CCI

CCI

CCI

| | |
|---|---|
| CCI | CCI |
| CCI | |
| CCI | CCI |
| CCI | CCI |
| CCI | |
| CCI | CCI<br>CCI |
| CCI | CCI |

AE, adverse event; CCI
SAE, severe adverse event

# 3 INVESTIGATIONAL PLAN - Core

## 3.1 Overall Study Design

This is a modular Phase I/II, open-label, multi-centre study in patients with advanced haematological malignancies with limited treatment options. Each module will evaluate the safety, tolerability, PK, and preliminary efficacy of AZD0466 as monotherapy or in combination with other treatments in the patient population.

For further details refer to the individual modules.

## 3.2 Endpoints and Associated Variables

### 3.2.1 Efficacy Variables

Disease assessments will be based on bone marrow biopsy and aspirate, peripheral blood collected for complete blood count (CBC), and blood smear with leukaemic blast count, if clinically indicated. Baseline assessments will be performed within 28 days before the first dose/administration of study medication and ideally as close as possible to the start of study treatment. Post-baseline disease assessments will be performed following the SoA in Tables 14, 15 and Tables 21, 22 in the study protocol.

In case of unscheduled disease assessments, these will also be included into the analysis.

#### 3.2.1.1 Response Evaluation Criteria – AML

Patients will be assigned to a response category by the investigator according to the criteria described in Appendix J in the study protocol for AML as for Module 1 Part A:

- CR (Complete remission),
  - CRmrd- (Complete remission without minimal residual disease negativity),
  - CRmrd+ (Complete remission without minimal residual disease positivity),
  - CRmrd unknown (Complete remission with minimal residual disease unknown),
- CRi (CR with incomplete recovery),
- MLFS (Morphologic leukaemia-free state),
- PR (Partial remission),
- CRc (Cytogenetic CR, Part A only),
- CRm (Molecular CR, Part A only),
- SD (Stable disease),
- PD (Progressive disease),
- Treatment Failure, as:
  - Resistant disease,
  - New extramedullary disease,
  - Resistant disease or new extramedullary disease,
  - Death in aplasia,
  - Death from indeterminate cause,
- Relapse.

This assignment is regardless of whether visits were scheduled or unscheduled and also regardless of whether a patient discontinues study intervention or receives another anticancer therapy.

Reasons for overall response classification (supporting data leading to the classification of response, multiple options may be selected) will be listed as follows:

- Radiological imaging,
- Bone marrow,
- Peripheral blood,
- Other.

Reasons for determining treatment failure, relapse, or disease progression (multiple options may be selected) will be listed as follows:

- Increased/new extramedullary disease,
- Increased blast cells in bone marrow,
- Increased blast cells in peripheral blood,
- Other.

#### 3.2.1.2 Response Evaluation Criteria – ALL

Patients will be assigned to a response category by the investigator according to the criteria in Appendix K in the study protocol for ALL as:

- CR (Complete remission),
- CRi (CR with incomplete recovery),
- PR (Partial remission),
- Treatment Failure (specified as either Resistant Disease, Death in aplasia, or Death from indeterminate cause),
- Relapse (specified as either Relapse from CR, Relapse from CRi, or Relapse from PR).

This assignment is regardless of whether visits were scheduled or unscheduled and also regardless of whether a patient discontinues study intervention or receives another anticancer therapy.

Reasons for overall response classification (supporting data leading to the classification of response, multiple options may be selected) will also be summarised as follows:

- Radiological imaging,
- Bone marrow,
- Peripheral blood,
- Other.

Reasons for determining treatment failure or relapse (multiple options may be selected) will also be summarised as follows:

- Increased/new extramedullary disease,
- Increased blast cells in bone marrow,
- Increased blast cells in peripheral blood,
- Other.

<u>Extramedullary disease</u>

Extramedullary disease status will be obtained by assessments made by the investigator based on the use of CT/MRI/PET scans during the screening period within 28 days before the first dose/administration of study medication. Post-baseline assessments for the response status (C1/C2) will be performed following the SoA in Tables 14, 15 and Tables 21, 22 in the study protocol.

Patients with hepatosplenomegaly at baseline will have spleen and liver measured at screening and at all subsequent response evaluations

For further details for derivation of the extramedullary disease status refer to the study protocol Appendix K.

For further details on efficacy variables refer to the individual modules.

### 3.2.2 Pharmacokinetic Variables

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

### 3.2.3 Safety and Tolerability Variables

The primary objective is to assess the safety and tolerability of the AZD0466 in patients with advanced haematological malignancies.

The following assessments will be performed:

- Adverse event (AE) assessments,
- Clinical chemistry (including creatine phosphokinase) and haematology as described in Section 4.14.6,
- Amylase and lipase, coagulation indices, serum immunoglobulins, urinalysis, cardiac troponin and BNP (or NTproBNP), cortisol, ACTH and TSH parameters described in Section 4.14.6,
- Vital signs (systolic blood pressure [SBP] and diastolic blood pressure [DBP], pulse rate, oral body temperature), height and weight,
- 12-lead Electrocardiograms (ECG),
- Tumour lysis syndrome (TLS; clinical and laboratory assessments),
- Eastern Cooperative Oncology Group performance status (ECOG PS),
- Left ventricular ejection fraction (echocardiograms [ECHO] / multi-gated acquisition scan [MUGA]).

The full list of laboratory measurements performed during the study that are used to evaluate safety and tolerability variables can be found in Table 1 and Table 2.

For further module specific definitions of the safety and tolerability variables refer to the individual modules.

## 4 STATISTICAL METHODS - Core

### 4.1 Data Quality Assurance

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

### 4.2 General Presentation Considerations

The following considerations will be applicable to all modules.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, 25th and 75th percentiles (where appropriate), minimum, maximum and number of observations. For log-transformed data it is more appropriate to present geometric mean (gmean), geometric coefficient of variation (CV), median, minimum and maximum.

With continuous data, any calculation of descriptive statistics or other derived parameters will be performed without rounding, but only for presentation in the output. The original values, as to be presented for minimum and maximum, will be rounded as applicable in order to enable readability

with 5 to a maximum of 7 significant digits depending on the dimensional range of the original data, e.g.:

| Data of a range | | Presented as | |
|---|---|---|---|
| From | To | Minimum | Maximum |
| 12.34 | 56.789 | 12.340 | 56.789 |
| 1234.5678 | 12345.6789 | 1234.6 | 12345.7 |
| 0.1234 | 1234.5678 | 0.123 | 1234.568 |

The mean, median and geometric mean (gmean) will be rounded to one additional decimal place compared to the presentation of the original data. The SD will be rounded to two additional decimal places compared to the presentation of the original data. Geometric CV will be presented with one decimal place. The maximum number of decimal places reported will be four for any summary statistic.

Categorical data will be summarized by frequency counts and percentages for each category.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Unless otherwise stated, percentages will be calculated out of the analysis set total and each dose level/cohort as appropriate for the respective module.

Confidence intervals (CIs) and p-values, when presented, will generally be constructed at 2-sided 80% and 95% level. CIs will be presented to one additional place than presented for the original data.

Unless otherwise stated, summaries will be presented by dose level or by cohort, as applicable for the respective module.

Baseline measurements and change from baseline variables

Baseline will generally be the last value obtained prior to the first dose of study medication. Alternatively, 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), the average will be taken as a baseline value. In the scenario where there are two assessments pre-dose on day 1, one with time recorded and the other without time recorded, the one with time recorded will be selected as the baseline value. Where safety data are summarized over time, study day will be calculated in relation to date of first dose.

For assessments performed on the day of first dose for which time is not captured a nominal pre-dose indicator as the variable label will serve as evidence that the assessment occurred prior to first dose. Assessments on the day of first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to first dose if such procedures are required by the protocol to be conducted before first dose.

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

$$\text{post-baseline value - baseline value}$$

Percent change from baseline will be calculated as:

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

For considerations for analysis of pharmacokinetic data refer to sections 4.13.1, and 4.13.2.

## 4.3 General Variables

### 4.3.1 Data cut-off

A data cut-off is not applicable. There will be one data analysis performed for both modules after the data base was locked. All data will be used as available.

### 4.3.2 Study Day Definitions

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

For visits (or events) 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).

"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.

### 4.3.3 Time Windows

Time windows for a reassignment of visits are not applicable for this study. The visit schedule is defined with the study protocol and the eCRF is set up to follow this scheme as defined. If measurements are repeated outside of the current schedule due to abnormalities, these will be recorded as unscheduled visits. Extreme value summaries use all values collected after baseline, including those collected at unscheduled visits. By-visit summaries only consider the scheduled assessments.

Listings will display all values contributing to each scheduled time point and unscheduled visits for a patient.

### 4.3.4 Handling of Missing Data

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

#### 4.3.4.1 Imputations of Partial Dates

**Concomitant medication and adverse events start dates**

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

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

**Concomitant medication and adverse events end dates**

- Missing day: imputed with the last day of the month, unless month and year are the same as month and year of last dose of study treatment, then imputed with the last treatment date in that month.
- Missing day and month: imputed with the 31st of December unless the year is the same as the year of last dose of study treatment, the imputed with the last treatment date in that year.
- Completely missing: no date imputed (the event is assumed to be ongoing).

No study day or duration will be calculated for imputed dates.

#### 4.3.5 Imputation Rules for Laboratory Values Outside of Quantification Range

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

### 4.4 Software

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

PK analyses will be produced using Phoenix® WinNonLin (WNL) version 8.1 or later in a secure and validated environment.

### 4.5 Analysis Sets

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

### 4.6 Study Patients

#### 4.6.1 Disposition of Patients

Patient disposition from screening to study completion will be listed and summarised for the Enrolled analysis set. Summaries will include:

- Number of patients screened (informed consent received)
- Number of subjects assigned to study treatment
- Number and percentage of patients who did not receive study treatment (including reasons)
- Number and percentage of patients who received study treatment
- Number and percentage of patients who completed study treatment (including reasons for those that did not)
- Number and percentage of patients who completed study (including reasons for those that do not)

Study treatment discontinuations will be listed, including dose level/cohort/study treatment as appropriate for the respective module, the date of study treatment discontinuation, total treatment duration (days), actual treatment duration (days) and reason for discontinuation. Total treatment duration and actual treatment duration will be derived as described in Section 4.14.1.

An additional listing will be provided for study completion status.

A summary of the number and percentage of patients that were screened will be presented by country and site.

#### 4.6.2 Protocol Deviations

General protocol deviation categories will be programmatically pulled from the electronic case report form (eCRF) data. These deviations and deviations identified from monitoring notes or reports will be reviewed and assessed by AZ on a case by-case basis to determine importance. 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 treatments. All decisions on importance will be made ahead of database lock and will be documented.

The important protocol deviations will be listed and summarised by dose level /cohort on the safety analysis set.

A full list of protocol deviations can be found in the study-specific protocol deviation specification.

#### 4.6.2.1 Important Protocol Deviations

According to ICH E3 guidelines version dated 1995 (ICH 1995),

"Protocol deviations consist of any change, divergence or departure from the study design or procedures defined in the protocol. Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety or well-being."

For this study, the following 4 general categories will be considered IPDs and will be summarised in the CSR:

- Deviation 1: Patients who received treatment and who deviated from the entry criteria in the study protocol.
- Deviation 2: The patient met discontinuation criteria but did not discontinue AZD0466 (e.g. patient withdrew consent, patient became pregnant).
- Deviation 3: The patient received a prohibited concomitant medication or procedure as detailed in Section 6.5.1 of the study protocol or any other concomitant medication or procedure which, upon physician review of all medications and procedures prior to database lock , is considered to have a potential effect on study outcomes.
- Deviation 4: Administration of study treatments, treatment compliance or dose level assignment was not according to protocol, and considered to have a potential effect on study outcomes.

Details for the protocol deviations criteria with potential to be assessed as an IPD will be specified in the protocol deviations specifications document.

#### 4.6.2.2 Monitoring of Important Protocol Deviations

Programmable protocol deviations will be detected from the data recorded in the clinical database and will be reviewed at regular protocol deviations review meetings. At this meeting, the programmatically-derived protocol deviations will be checked to ensure that they have been correctly classified as major or minor protocol deviations.

On an ongoing basis throughout the study, monitoring notes or summaries will also be reviewed to determine any important post entry deviations that are not identifiable via programming.

If the number of deviations which are considered to have the potential to impact the primary analysis is considered important, sensitivity analyses may be performed on subgroups. This will be decided during the data review meeting and before the database lock.

The final classification of IPDs will be made prior to database lock or data cut-off for final analysis. Any other deviations from monitoring notes or reports will be reported in an appendix to the CSR.

### 4.7 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarised and listed for all patients in the Safety analysis set by dose level/cohort as appropriate:

- Demographic characteristics (age [years], age group [< 65 years; ≥ 65 years], sex [female; male], race, ethnicity and country); height (cm), weight (kg)
- Any other patient/disease characteristics at baseline as specified below:
    - Disease type,
    - WHO classification of acute leukaemia,
    - Molecular and cytogenetic characteristics of AML/ALL,
    - Eastern Cooperative Oncology Group (ECOG) performance status,
    - Extramedullary disease will be listed for target/non-target lesions for ALL.

### 4.8 Medical/Surgical History

Medical history and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Disease related medical history will be listed and the number and percentage of patients with any disease-related medical history will be summarised for the Safety analysis set by system organ class (SOC) and preferred term (PT), by dose level/cohort and overall as appropriate.

Surgical history will be summarised, if applicable.

### 4.9 Prior Treatments for Leukaemia

Prior therapies are defined as started and stopped prior to the first dose of the study treatment based on imputed start and stop dates. Incomplete therapy start and stop dates will be imputed as detailed in section 4.3.4.1.

Radiotherapy and all cancer therapies prior to the study will be listed.

The following summaries will be produced for prior therapies for leukaemia disease under study:

- Prior anti-cancer therapy class
- Prior anti-cancer radiotherapy
- Number of prior lines of anti-cancer therapy
- Number of prior regimens of anti-cancer therapy
- Anti-cancer therapy agent by ATC and generic drug name

Treatment status (Consolidation, Palliative, Maintenance, Induction Therapy) will be listed.

In addition to prior therapies for leukaemia, post-study cancer treatment will be listed. Post-study anti-cancer treatments are defined as treatments started after a patient discontinued study treatment.

### 4.10 Previous and Concomitant Medications and Other Treatments

Treatments received prior to, concomitantly or post-treatment will be coded using the World Health Organisation-Drug Dictionary (WHODRUG) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

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 4.3.4.1.

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

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

All concomitant medication will be listed by patient and will include the reported name, coded name , (ATC), route of administration, dose, frequency, start date/time, duration and indication (PT). Concomitant medication will be summarised by ATC and PT, dose level/cohort as appropriate.

All prior, concomitant and post study treatment medication data (including surgical procedures) will be listed. Missing coding terms (ATC or PT) will be listed and summarised as uncoded terms.

All listings and tables will be based on the Safety analysis set.

### 4.11 Disallowed Concomitant Medications

Patient may have received prohibited concomitant medication as detailed in Section 6.5.2 of the study protocol or any other concomitant medication which, upon physician review of all medications and procedures prior to database lock, is considered to have a potential effect on study outcomes.

Disallowed concomitant medications will be summarised and listed.

### 4.12 Efficacy Evaluation

Refer to the individual modules.

### 4.13 Pharmacokinetics

#### 4.13.1 Pharmacokinetic Concentrations

Plasma concentrations of total and released AZD4320 will be listed by actual and relative (to dose administration) sampling time. The following summary statistics will be presented for the concentrations and PK parameters at each time point separately per cohort and actual dose level:

- 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($s^2$)-1], where s is the standard deviation of the data on a logarithmic scale)
- Arithmetic Mean
- Arithmetic 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 (gSD calculated as exp[μ±s])
- 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.

### 4.13.2 Pharmacokinetic Parameters Calculation and Summary

Derived PK parameters will be summarized by cycle, separately per cohort and actual dose level. 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 $\sqrt{}$ [exp($s^2$)-1], where s is the standard deviation of the data on a logarithmic scale)
- Arithmetic mean calculated using untransformed data
- Arithmetic SD calculated using untransformed data
- Minimum
- Median
- Maximum
- Number of observations

The descriptive statistics for diagnostic parameters are n, arithmetic mean, SD, median, min, and max.

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.

#### 4.13.3 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.

#### 4.13.4 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.

### 4.14 Safety and Tolerability Evaluation

Refer to the individual modules.

#### 4.14.1 Exposure and treatment administration

Exposure to investigational product i.e. total amount of study drug received will be listed for all patients.

Total treatment duration will be summarized by the following: mean, standard deviation, minimum, maximum, median and number of observations. Exposure is also measured by the number of cycles received. A cycle corresponds to a period of 28 days from cycle 2 and 35 days for cycle 1. If a cycle is prolonged due to toxicity, this should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered. In addition, the number and percentage of

patients with at least one dose reduction will be presented separately for the initial period of evaluability defined as 35 days and for any cycle in the study.

Relative dose intensity (RDI) of AZD0466 will be derived as the percentage of the actual dose delivered relative to the intended dose up to treatment discontinuation as:

$$RDI(\%) = 100 \times d/D$$

where:

d is the actual cumulative dose delivered up to the last dosing, and

D is the intended cumulative dose up to the last day of dosing
(i.e. that would have been delivered without a modification of the dose or schedule).

Summaries by mean, standard deviation, minimum, maximum, median and number of observations will be produced for RDI of AZD0466.

### 4.14.2 Dose limiting toxicities (DLTs)

A DLT is defined as an AE or abnormal laboratory value that meets the predefined study DLT criteria as described in Section 11.4.7.2 in the study protocol. The DLT evaluation period is defined from first dose of study treatment, up to the end of Cycle 1 (Day 35). DLTs occurring during this period will be used for determination of the maximum tolerated dose (MTD) during Part A in Module 1.

The number of patients evaluable for determination of DLTs and the number of patients with any DLT (and their categorisation) during the DLT evaluation period will be summarised by dose level/cohort, and by SOC and PT, as appropriate.

The listings and tables will be based on the DLT-evaluable analysis set.

### 4.14.3 Definition of Maximum Tolerated Dose and Definition of Recommended Phase II Dose

The MTD evaluation will be based on the DLT-evaluable population. The MTD will be determined by isotonic regression analysis applied to DLT rates observed during the dose-escalation phase. The estimated MTD will be selected as the dose with the smallest absolute value of difference between the estimated DLT rate and the target DLT rate of 30% among all doses. If 2 or more doses tie for the smallest difference, the following rules will be applied:

If the estimated DLT rate is < 30% for all doses, then select the higher dose among the tied doses

If the estimated DLT rate for the tied doses are a combination of < 30% and > 30% then select the higher dose among the tied doses

If the estimated DLT rate is > 30% for all doses, then select the lower dose among the tied doses.

The MTD evaluation will not be part of this analysis and thus related methods are not further be described in this analysis plan. The RP2D and schedule will be determined in discussion among the SRC (Appendix A 5 of the study protocol) and the sponsor. Observations related to PK, PD, and AEs may be included in the rationale supporting the RP2D and schedule.

### 4.14.4 Adverse Events

Any AE occurring on or after first dose of study treatment and within 28 days after discontinuation of study treatment will be included in the AE summaries. Any AEs in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be

flagged in the data listings. AEs occurring before first dose of study treatment or after 28 days after discontinuation of study treatment will be listed separately, but not included in the summaries.

AEs will be coded using the most recent Medical Dictionary for Regulatory Activities (MedDRA) Version as available at data cut-off and will be graded according to the National Cancer Institute of Common Terminology Criteria for AEs (CTCAE version 5.0).

**AEs of special interest**
In this study, the following are considered to be AESIs:

- Tumour lysis syndrome (Appendix G of the study protocol)
- Hepatotoxicity, including potential Hy's Law, drug-induced liver injury (DILI), and bilirubin increase with transaminase (ALT or AST or both ALT and AST) increase
- QRS amplitude decrease

All AEs will be listed individually by patient and dose level/cohort as appropriate with the inclusion of the patient identifier, centre, country, age, race, sex, preferred term, reported term, time of onset, duration (days), CTCAE, seriousness (serious/non-serious), action taken (dose not changed, dose increased, dose reduced, drug interrupted, drug permanently discontinued, N/A), outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved), related assessed by investigator, DLT as well as a flag in the case of AEs occurring after additional cancer therapy. AEs of special interest (AESI) will be listed.

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

- Overall summary of adverse events for the categories:
  - Any AE
  - Any SAE
  - Any SAE with outcome death
  - Any AE leading to discontinuation of AZD0466
  - Any possibly related AE
  - Any possibly related SAE
  - Any AE leading to AZD0466 dose reduction
  - Any AE leading to AZD0466 dose interruption
  - Any AE of >= CTCAE grade 3
  - Any SAE and/or >= CTCAE grade 3 AE
  - Any AE classified as a DLT
  - Any possibly related deaths
- AEs by SOC and PT
- AEs sorted by decreasing frequency by PT
- AEs by SOC, PT and maximum reported CTCAE grade
- AEs of CTCAE grade 3 or higher by SOC and PT
- AEs 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.
- Time to onset of first AE (days) by SOC and PT
- Duration of first AE (days) by SOC and PT
- AEs leading to hospitalisation by SOC and PT
- AEs by PT and maximum reported CTCAE grade

- AEs by PT and relationship to study treatment
- AEs with outcome death by SOC and PT
- AEs assessed by investigator as possibly related with outcome death by SOC and PT
- SAEs by SOC and PT
- SAEs leading to discontinuation of study treatment by SOC and PT
- SAEs leading to discontinuation of study treatment assessed by investigator as possibly related to study treatment by SOC and PT
- Non-serious AEs sorted by decreasing frequency by PT.
- SAEs assessed by investigator as possibly related to study treatment by SOC and PT
- AEs leading to discontinuation of study treatment by SOC and PT
- AEs assessed by investigator as possibly related to study treatment leading to discontinuation of study treatment by SOC and PT
- AEs leading to reduction of study treatment by SOC and PT
- AEs leading to interruption of study treatment by SOC and PT

For patients with multiple AEs of the same SOC and/or PT, only the AE with the highest CTCAE grade per system organ class and preferred term will be included in the summaries presented by maximum CTCAE grade. Similarly, for multiple AEs differing in causality, only the AE with causality will be included in by-causality summaries. If causality is missing, the AE will be considered related in all summaries.

In summaries including SOC or PT, the summaries are sorted by international order for SOC and in alphabetical order for PT.

The following summaries for the number and percentage of patients will be created for AESIs if applicable:

- By PT
- By outcome
- By time of resolution
    - On-treatment, which is defined as AEs with onset date on or after first study treatment, but before or on date of end of treatment;
    - Follow-up, which is defined as AEs with onset after, but within 28 days after end of treatment;
    - Post-treatment, which is defined as AEs with onset after 28 days after end of treatment.

### 4.14.5 Deaths

A summary will be provided with the number and percentage of patients who died, and death event was categorised as:

- AEs with outcome of death only
- Related to disease under investigation only
- Both related to disease under investigation and an AE with outcome of death only
- AEs with a start date after 28 days after treatment discontinuation with an outcome of death
- Other deaths

A corresponding listing will also be produced.

### 4.14.6 Clinical Laboratory Evaluation

All local laboratory results collected will be listed according to the SoA in Tables 14, 15 and Tables 21, 22 in the study protocol.

Summaries for safety laboratory will include the parameters as specified in Table 1 and Table 2.

**Table 1 Laboratory Safety Variables - Clinical Chemistry**

| | | |
|---|---|---|
| Albumin | Cholesterol[a] | Magnesium |
| Alkaline phosphatase | C-reactive protein | Phosphate |
| Alanine aminotransferase | Creatinine | Potassium |
| Amylase[b] | Gamma-glutamyl transferase | Sodium |
| Aspartate aminotransferase | Glucose[a] | Triglycerides[a] |
| Bicarbonate | Glutamate dehydrogenase | Total protein |
| Bilirubin (total and direct) | Lactate dehydrogenase | Chloride |
| Blood urea nitrogen | Lipase[b] | Uric acid |
| Corrected calcium | | |

[a] Fasting cholesterol, triglyceride and glucose values are not required. However, if non-fasting values are abnormal, a repeat sample should be obtained when the patient is fasting.

[b] Collected at screening, pre-infusion on each dosing day, and end of treatment visit.

**Table 2 Laboratory Safety Variables - Haematology**

| | |
|---|---|
| Absolute leucocyte differential count: neutrophils, lymphocytes, monocytes, basophils, eosinophils | CCI |
| Blood (B)-haemoglobin | Haematocrit |
| Leucocytes | Platelet count |

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

All clinical laboratory results will be listed.

For all continuous laboratory assessments, the absolute values and the change from baseline will be summarised using descriptive statistics at each time point by dose level/cohort as appropriate.

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

Liver biochemistry test results over time for patients with elevated ALT or AST (≥ 3 x ULN) and elevated bilirubin (≥ 2 x ULN,) regardless of whether or not these elevations occurred at the same visit, or ALT or AST of ≥ 5 x ULN, will be tabulated and plotted.

All parameters as used for summaries including amylase and lipase, coagulation indices, serum immunoglobulins, urinalysis, cardiac troponin and BNP (or NTproBNP), clinical and laboratory assessments for TLS, Cortisol, ACTH and TSH parameters will be listed as appropriate.

Following 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.

### 4.14.7 Vital Signs

The following vital signs will be assessed and listed:

- Systolic blood pressure (SBP) [mmHg]
- Diastolic blood pressure (DBP) [mmHg]
- Pulse rate (bpm)
- Oral body temperature (°C)
- Respiration rate (breaths/min)
- Body weight (kg)

Change from baseline in vital signs variables will be calculated for each post-dose visit.

Descriptive statistics for absolute values and changes from baseline will be presented by dose level/cohort as appropriate.

Blood pressure and pulse rate will be plotted as subject profiles.

### 4.14.8 ECGs

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

- PR-interval (msec).
- QRS-duration (msec).
- QT-interval (msec).
- QT-interval corrected using the Fridericia correction formula (QTcF) (msec).
- RR-interval (msec).
- Heart rate (beats per minute [bpm]).

The ECG will be evaluated by the Investigator as ‘Normal’, ‘Abnormal.

All ECG parameters will be listed by patient including changes from baseline for numeric ECG parameters.

Descriptive statistics for the means of the triplicate ECG measurements in absolute values and changes from baseline will be presented by dose level/cohort as appropriate. The values used for this summary are the average of the three measurements of the triplicate ECG.

A shift table for the overall ECG assessment from baseline to the worst (abnormal) on-treatment assessement will be created.

Subject profiles will be plotted for the means of the triplicate ECG measurements in absolute values.

QTcF outliers (defined as values following study treatment that are greater than 470 msec or increases from baseline greater than 30 msec) will be summarised using cumulative counts and percentages under the following categories:

- Absolute value > 470 msec

- Absolute value > 480 msec
- Absolute value > 500 msec
- Change from baseline > 30 msec
- Change from baseline > 60 msec
- Absolute value > 470 msec and change from baseline > 30 msec
- Absolute value > 500 msec and change from baseline > 60 msec.

### 4.14.9 LVEF

Descriptive statistics for left ventricular ejection fraction (LVEF) for absolute values and changes from baseline will be presented by dose level/cohort as appropriate.

Summary tabulations of frequencies will be presented for:

- Baseline CTCAE grade, as defined by:
  - ≥ 50% (CTCAE Grade 0)
  - 40% to < 50% (CTCAE grade 2)
  - 20% to < 50% (CTCAE grade 3)
  - < 20% (CTCAE grade 4).
- Maximum on-treatment CTCAE grade, as defined by:
  - ≥ 50% (CTCAE Grade 0)
  - 40% to < 50% or 10 to 19% drop from baseline (CTCAE grade 2)
  - 20% to < 50% or 20 to 29% drop from baseline (CTCAE grade 3)
  - < 20% (CTCAE grade 4).

In addition, the results of (echocardiograms [ECHO] / multi-gated acquisition scan [MUGA]) scans for LVEF will be listed.

### 4.14.10 Eastern Cooperative Oncology Group Performance Status (ECOG PS)

ECOG performance status scores will be assessed at screening and before each dose of AZD0466 according to ECOG criteria as follows:

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

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

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

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

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

5 = Death.

The ECOG performance status will be listed and summarised as frequency counts by dose level/cohort and visit as appropriate.

### 4.14.11 Tumour lysis syndrome (TLS)

Table of key subject information for patients with tumour lysis syndrome will be provided. This listing will comprise

- Disease history (AML/ALL), age, gender, cohort
- Baseline risk of TLS as specified in Table 3
- WBC, LDH, BUN at baseline
- Allopurinol, and Rasburicase prophylaxis (identified by ATC-code list from prior or concomitant medications)
- Date and time of TLS assessment
- Parameters contributing to the laboratory TLS
- Parameters contributing to the clinical TLS with Cairo-Bishop Grade
- Overall Cairo-Bishop Grade (as assessed by the investigator)
- AE term and number, AE recorded as a DLT, AE serious, AE start and stop dates, and AE outcome.

**Table 3 Risk of tumour lysis syndrome**

| Malignancy | Risk of tumour lysis syndrome[a] | | |
|---|---|---|---|
| | **High** | **Intermediate** | **Low** |
| Acute myeloid leukaemia | WBC ≥ 100 $\times 10^9$/L | WBC ≥ 25 and ≤ 100 $\times 10^9$/L<br>or<br>WBC < 25 $\times 10^9$/L and<br>LDH ≥ 2x ULN | WBC < 25 $\times 10^9$/L and LDH < 2x ULN |
| Acute lymphoblastic leukaemia | WBC ≥ 100 $\times 10^9$/L and<br>LDH ≥ 2x ULN | WBC < 100 $\times 10^9$/L and<br>LDH < 2x ULN | - |

[c] WBC < 10 $\times 10^9$/L is required for study eligibility and hydroxyurea is permitted during screening and Cycle 1 to achieve this; consequently patients will be intermediate or low risk of TLS.

Risk classification adapted from MD Anderson Cancer Center guidance.

Summary tabulations of frequencies for Overall Cairo-Bishop Grade (as assessed by the investigator) will be presented at patient- and event-level for:

- Laboratory TLS
- Clinical TLS
- Cairo-Bishop TLS Grade
- TLS classified as a DLT

Time to first onset of Laboratory TLS and Time to first onset of Clinical TLS will be presented as categorical groupings by cycle, and as summary statistics, including Kaplan-Meier statistics (Q1, median and Q3).

### 4.14.12 Determination of Sample Size

Refer to the individual modules.

### 4.14.13 Interim Analyses

Refer to the individual modules.

# 5 INTRODUCTION – Module 1 Part A

Module 1 will evaluate the safety, tolerability, PK, and efficacy of AZD0466 as monotherapy. Part A is a dose escalation assessment of the safety and tolerability of AZD0466 to determine the recommended dose and schedule for further evaluation.

As Module 1 Part B was not initiated, Sections 6, 7 and 8 describe the analyses to be conducted for Module 1 Part A.

For further general study information refer to Section 1.

# 6 STUDY OBJECTIVES - Module 1 Part A

The core objectives and endpoints for the study are listed in Sections 2.1, 2.2, and 2.3; additional endpoints for Module 1 Part A are listed in Sections 6.1, 6.2, and 6.3.

## 6.1 Primary Objective

| Objectives | Endpoints/Variables |
|---|---|
| To assess the safety and tolerability of AZD0466 in patients with advanced haematological malignancies | DLT<br>MTD<br>RP2D and schedule |

DLT, dose-limiting toxicity; MTD, maximum tolerated dose; RP2D, recommended Phase II dose

## 6.2 Secondary Objectives

| Objectives | Endpoints/Variables |
|---|---|
| **Complete Response Rate (CR+CRi)** | |
| To estimate the preliminary antitumor activity of AZD0466 by assessment of Complete response rate (CR+CRi) in patients with advanced haematological malignancies | Complete response rate (CR+CRi) is defined as the proportion of patients who have a complete remission (CR) or incomplete haematological response (CRi), as determined by criteria described in Appendix J and Appendix K of the study protocol.<br>The analysis will include all dosed patients as intended.<br>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 CR+CRi, regardless of whether the patient withdraws from study treatment. Patients who go off treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in this evaluation.<br>The measure of interest is the estimate of CR+CRi. |
| **Time to Response (TTR)** | |
| To estimate the preliminary antitumor activity of AZD0466 by assessment of time to complete | Time to response is defined as the time from date of first dose until the date of first documented CR or CRi. |

| Objectives | Endpoints/Variables |
|---|---|
| response (TTR) in patients advanced haematological malignancies | The analysis will include all dosed patients as intended, who have a complete remission.<br>Patients who go off study treatment without a clinical response and receive a subsequent therapy and then respond will not be included.<br>The measure of interest is median TTR. |
| **Duration of Response (DoR)** | |
| To estimate the preliminary antitumor activity of AZD0466 by assessment of DoR in patients with advanced haematological malignancies. | DoR will be defined as the time from the date of first documented response (CR+CRi) until date of documented progression, relapse, failure (relapse and failure as determined by criteria described in Appendix J and Appendix K of the study protocol) or death due to any cause.<br>The analysis will include all dosed patients as intended who have a confirmed response (CR or CRi), regardless of whether the patient withdraws from study treatment or receives another anticancer therapy.<br>The measure of interest are the percentiles of DoR. |
| **Overall Survival (OS)** | |
| To estimate the preliminary antitumor activity of AZD0466 by assessment of OS in patients with advanced haematological malignancies. | OS is defined as time from date of first dose until the date of death due to any cause.<br>The comparison will include all dosed patients as intended, regardless of whether the patient withdraws from therapy or receives another anticancer therapy.<br>The measures of interest are the median OS and landmarks at 6 and 12 months of OS. |

ALL, acute lymphocytic leukaemia; AML, acute myeloblastic leukaemia; CR, complete remission; CRi, incomplete haematological response; DoR, duration of response; OS, overall survival; TTR, time to response

## 6.3 CCI [redacted]

| | |
|---|---|
| CCI [redacted] | CCI [redacted] |
| CCI [redacted] | CCI [redacted] |

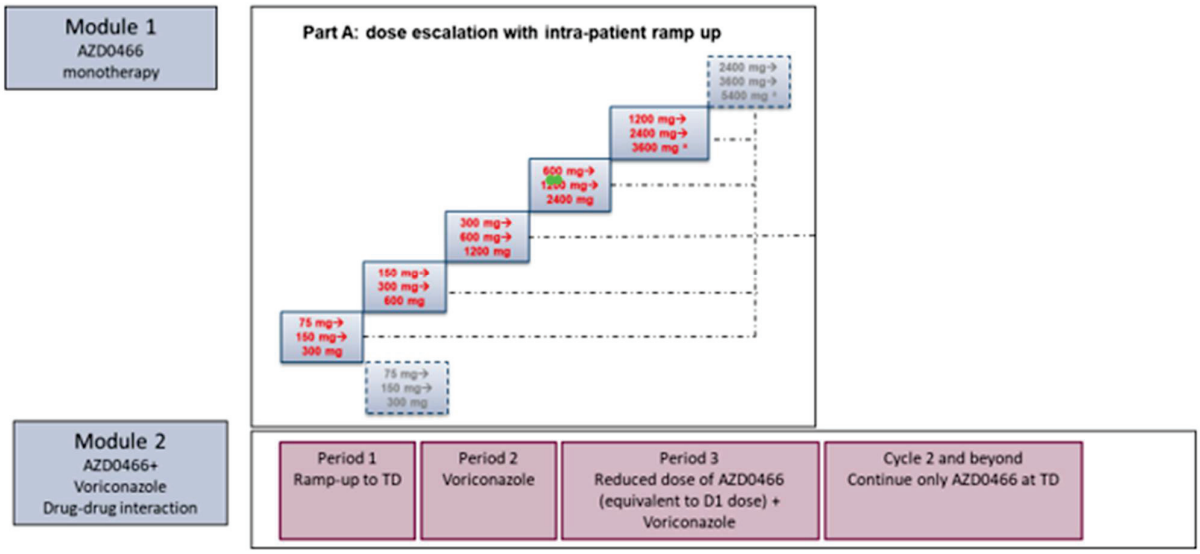

# 7 INVESTIGATIONAL PLAN - Module 1 Part A

## 7.1 Overall Study Design

Module 1 Part A is a Phase I dose escalation evaluation of AZD0466 monotherapy.

A visual representation of Module 1 is shown in Figure 1.

**Figure 1 Schema for Module 1**




[a] AZD0466 doses shown are illustrative. Actual doses will not exceed a 2-fold increase of a dose declared tolerable by the SRC, or the maximum feasible dose as specified in in the study protocol section 11.4.7.5.

Dotted paths contingent on emerging data.

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; DL, dose level; IA, interim analysis; MPN, myeloproliferative neoplasm; TP53, gene encoding tumour protein p53.

Part A, the dose escalation part of the study, will enrol up to 40 patients with a histologically confirmed AML or ALL to ensure 30 DLT-evaluable patients in total. At least 3 DLT-evaluable patients are required at each dose level and, up to 12 patients overall may be enrolled at each dose level. Up to additional 18 patients may be enrolled to backfill earlier cohorts at lower dose levels with the intent of enabling pre- and on-treatment peripheral blood samples and bone marrow aspirates and biopsies to aid characterisation of the PD of AZD0466 and to provide additional data on safety, tolerability, PK, and biological activity (n = 58 in total). If a dose escalation cohort and a backfill expansion cohort are simultaneously open to enrolment, precedence will be given to enrolment into the dose escalation cohort.

A SRC will be responsible for making recommendations for dose-escalation or de-escalation after each dose level, including decisions on opening cohorts for backfill, in accordance with the SRC charter. From day of target dose, a delay of at least 3 days will be mandatory between the first and second patient at each dose level. This separation between the dosing of patients will ensure that any acute toxic effects of the AZD0466 infusion will have sufficient time to be identified before additional patients are exposed. The intra-patient dose ramp-up and/or dose schedule for each cohort may be modified based on safety, PK, and PD findings of a previous 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.

## 7.2 Endpoints and Associated Variables

### 7.2.1 Efficacy Variables

For the definitions of the efficacy variables for the response evaluation criteria variables for ALL and AML, and extramedullary disease refer to the Section 3.2.1.

#### 7.2.1.1 Overall Survival (OS)

OS is defined as the time from date of first dose until the date of death from any cause. The analysis will include all dosed patients according to assigned dose, regardless of whether the patients withdraws from therapy or received another anticancer therapy. Patients who have not died during the course of the study will be censored at their last date known to be alive.

Survival follow-up phone calls or clinic visits will be made approximately every 1 month after last dose for all patients for survival until death, lost to follow-up, AstraZeneca closes the study or withdrawal of consent, whichever occurs first. 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.

For any OS analysis performed prior to the final OS analysis, in the absence of survival calls being made, it is necessary to use all relevant eCRF fields to determine the last recorded date on which the patient was known to be alive for those patients still on treatment (since SURVIVE module is only completed for patients off treatment if a survival sweep is performed). The last date for each individual patient is defined as the latest among the following dates recorded in the eCRF:

- AE start and stop dates
- Admission and discharge dates of hospitalisation
- Study treatment date
- End of treatment date
- Laboratory test dates
- Date of vital signs
- Disease assessment dates on eCRF
- Start and stop dates of alternative anticancer treatment
- Date last known alive on survival status eCRF
- End of study date.

#### 7.2.1.2 Peripheral Blood

Peripheral blood will be collected for complete blood count (CBC) (laboratory safety assessment) as indicated in the SoA in Tables 14, 15 in the study protocol. CCI [redacted]

#### 7.2.1.3 Extramedullary Disease

Refer to Section 3.2.1.2.

#### 7.2.1.4 Bone Marrow

Bone marrow core biopsy and bone marrow aspirate should be performed as specified in in the SoA in Tables 16, 17 in the study protocol.

- Screening (between Day -14 and -1)
- Cycle 1 Day 30 ± 1 day
- Cycle 2 and subsequent cycles between Days 23 to 28
- Disease progression or EoT visit

The disease progression sample collection may occur at the safety follow-up visit (if conducted in person) if not collected previously. Additional bone marrow or peripheral blood samples may be collected, as clinically indicated.

### 7.2.2 Pharmacokinetic Variables

Pharmacokinetic parameters will be calculated by non-compartmental analysis methods using Phoenix® WinNonlin® (Version 8.1) or higher as data applicable.

The PK parameters are calculated/estimated according to AstraZeneca standards.

PK analysis will, where data allow, be carried out using actual elapsed times determined from the PK sampling and dosing times recorded will be used in the database. If actual elapsed times are missing, nominal times may be used. Nominal sampling times may be used for any agreed interim PK parameter calculations and PK parameters will be derived using standard non-compartmental methods.

Where data allow, the following PK parameters for total and released AZD4320 will be derived from plasma concentrations supporting doses on Cycle 1 Day 8 and Cycle 2 Day 1.

**Plasma**

| | |
|---|---|
| $C_{max}$ | Maximum observed plasma (peak) drug concentration |
| $t_{max}$ | Time to reach peak or maximum observed concentration or response following drug administration |
| $\lambda z$ | Terminal rate constant, estimated by log-linear least squares regression of the terminal part of the concentration-time curve |
| $t_{1/2}\lambda z$ | Half-life associated with terminal slope ($\lambda z$) of a semi-logarithmic concentration-time curve |
| $AUC_{0-72}$ | Partial area under the plasma concentration-time curve from time 0 to 72 hours after the start of infusion (Cycle 1 Day 8 only) |
| $AUC_{0-36}$ | Partial area under the plasma concentration-time curve from time 0 to 36 hours after the start of infusion (to match urine collection interval) (Cycle 1 Day 8 only) |
| $AUC_{0-24}$ | Partial area under the plasma concentration-time curve from time 0 to 24 hours after the start of infusion (to support comparisons between C1D8 and C2D1) |
| $AUC_{last}$ | 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 administered AZD4320 dose in mg |
| Dose normalised $AUC_{0-24}$[a] | Area under the plasma concentration-time curve from time 0 to 24 hours after the start of infusion divided by the administered AZD4320 dose in mg |
| Dose normalised $AUC_{0-72}$[a] | Area under the plasma concentration-time curve from time 0 to 72 hours after the start of infusion divided by the administered AZD4320 dose in mg (Cycle 1 Day 8 only) |
| Dose normalised $C_{max}$[a] | Maximum observed plasma (peak) drug concentration divided by the administered AZD4320 dose in mg |

[a] Calculated for total AZD4320 only; AZD4320 dose calculated as 29% w/w of the AZD0466 dose in mg, based on average batch results, unless an alternate value is specified.

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) |

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 $\lambda_z$ 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 $\lambda_z$ will be discussed in CSR.

**Urine**

Data permitting, the following urine PK parameters will be calculated for total AZD4320 for Cycle 1 Days 1, 4, and 8, as appropriate:

**Table 4 Urine PK parameters**

| | |
|---|---|
| Ae(t1-t2) | Cumulative and by interval amount of unchanged drug excreted in urine from time t1 to t2 |
| fe(t1-t2) | Cumulative and by interval percentage of adjusted AZD4320 dose excreted unchanged in urine from time t1 to t2. For fe, adjusted dose will be calculated as (AZD0466 dose / AZD0466 mol weight * AZD4320 mol weight) |
| CLR | Renal clearance of drug from plasma (Day 8 only) |

Additional PK parameters may be calculated as appropriate.

### 7.2.3 Safety and Tolerability Variables

Part A

The primary objective of Part A is to assess the safety and tolerability, describe the DLTs, and identify the MTD and/or RP2D of AZD0466 in patients with advanced haematological malignancies.

As referenced in Section 3.2.3 the safety assessments performed will be:

- Adverse event (AE) assessments
- Clinical chemistry (including creatine phosphokinase) and haematology as described in Section 4.14.6.
- Amylase and lipase, coagulation indices, serum immunoglobulins, urinalysis, cardiac troponin and BNP (or NTproBNP), clinical and laboratory assessments for TLS, cortisol, ACTH and TSH parameters described in Section 4.14.6.
- Vital signs (systolic blood pressure [SBP] and diastolic blood pressure [DBP], pulse rate, oral body temperature), height and weight
- 12-lead Electrocardiograms (ECG)
- Tumour lysis syndrome (TLS)
- Eastern Cooperative Oncology Group performance status (ECOG PS)
- Left ventricular ejection fraction (echocardiograms [ECHO] / multi-gated acquisition scan [MUGA]).

The full list of laboratory measurements performed during the study that are used to evaluate safety and tolerability variables can be found in Table 1 and Table 2.

# 8 STATISTICAL METHODS - Module 1 Part A

## 8.1 Data Quality Assurance

Refer to Section 4.1.

## 8.2 General Presentation Considerations

Refer to Section 4.2.

## 8.3 General Variables

### 8.3.1 Study Day Definitions

Refer to Section 4.3.2.

### 8.3.2 Time Windows

Refer to Section 4.3.3.

### 8.3.3 Handling of Missing Data

Refer to Section 4.3.4.

### 8.3.4 Imputation Rules for Laboratory Values Outside of Quantification Range

Refer to Section 4.3.5.

## 8.4 Software

Refer to Section 4.4.

## 8.5 Analysis Sets

Details of the analysis sets are presented in Table 5.

**Table 5 Analysis Sets – Module 1**

| Population/Analysis set | Description |
|---|---|
| Screened | All patients that signed the informed consent form (ICF) |
| Safety | All patients who received at least one dose of AZD0466 |
| Intention-to-treat | All patients who received at least one dose of AZD0466 |
| Evaluable for Response | All patients who have received at least 3 doses of AZD0466 at the target dose level in Cycle 1 |
| DLT-evaluable | Patients enrolled in the dose-escalation part of Module 1 that have received at least 3 doses of AZD0466 at the target dose level (75% of target doses from Day 8 to Day 29 in Cycle 1) and have completed the safety follow-up through the 35-day DLT evaluation period<br>Or<br>Have experienced a DLT during the 35-day DLT evaluation period in Cycle 1. |
| Pharmacokinetics | Dosed patients with at least one reportable plasma concentration and no important AEs or protocol deviations that may impact PK |

A summary on which analysis set will be used for each outcome variable is provided in Table 6.

**Table 6 Summary of outcome variables and analysis sets**

| Outcome variable | Analysis Set |
|---|---|
| ***Study Population/Demography Data*** | |
| Disposition | Enrolled |
| Demography and baseline characteristics | Safety |
| Important protocol deviations | Safety |
| Medical History | Safety |
| Prior/Concomitant Medication | Safety |
| ***Safety data*** | |
| Exposure | Safety |
| Adverse Events | Safety |
| Laboratory measurements | Safety |
| Vital Signs/ECG/Physical examination | Safety |
| ECOG PS | Safety |
| DLTs | DLT-evaluable |
| ***Efficacy Data*** | |
| CR rate | Evaluable for response; Intention-to-treat |
| TTR | Evaluable for response |
| DoR | Evaluable for response |
| OS | Intention-to-treat |
| ORR | Evaluable for response; Intention-to-treat |
| ***Pharmacokinetics*** | |
| Pharmacokinetic variables | PK |

CR complete response; DLT dose-limiting toxicity; DoR duration of response; ECOG PS Eastern Co-operative Oncology Group performance status; OS overall survival; PK pharmacokinetic.

The number of enrolled patients included/excluded from each of the analysis sets will be summarized. Patients and data excluded from each analysis set will be listed with the reason for exclusion.

## 8.6 Study Patients

### 8.6.1 Disposition of Patients

Refer to Section 4.6.1.

### 8.6.2 Protocol Deviations

Refer to Section 4.6.2.

## 8.7 Demographics and Baseline Characteristics

Refer to Section 4.7.

## 8.8 Medical/Surgical History

Refer to Section 4.8.

## 8.9 Concomitant Medications and Other Treatments

Refer to Section 4.10.

## 8.10 Efficacy Evaluation

The preliminary antitumor activity of AZD0466 will be estimated using the following endpoints:

- Complete response,
- OS.

All of the collected response related data, such as from complete blood count (CBC), extramedullary disease status, bone marrow core biopsy and aspirate will be listed for all patients in the Intention-to-treat analysis set. Summaries will not be produced.

### 8.10.1 Analysis and Data Conventions

No hypotheses are planned to be tested.

#### 8.10.1.1 Multi-centre Studies

No adjustments for centre will be performed.

#### 8.10.1.2 Adjustments for Covariates

No adjustments for covariates will be performed.

#### 8.10.1.3 Handling of Dropouts or Missing Data

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

### 8.10.2 Primary Efficacy Endpoints

#### 8.10.2.1 Complete Response (CR+CRi) Rate

Complete response rate (CR+CRi) for AML and ALL patients is defined as the proportion of patients with best response as complete remission (CR) or incomplete haematological response (CRi), as determined by criteria described in Section 3.2.1 and in Appendix J and Appendix K in the study protocol. Any treated patient who has not satisfied the criteria for CR or CRi will be treated as a non-responder for this analysis.

Data obtained from first dose up until treatment failure or disease progression, or the last evaluable assessment in the absence of treatment failure or disease progression, will be included in the assessment of CR+CRi, regardless of whether the patient withdrew from study treatment.

The complete response rate will be presented along with all remaining response categories, as defined in Section 3.2.1 by means of the proportion (%).

The analyses will include all patients from the Evaluable for Response analysis set. Patients who went off treatment without a response or who received a subsequent therapy after treatment failure or disease progression, and then respond will not be included as responders in this evaluation.

Secondarily, the analyses will be repeated for the Intention-to-treat analysis set, for that the denominators for the calculation of percentages will refer to the number of patients in the Intention-to-treat analysis set. Patients who are not evaluable for response analysis will not be assigned to a response category and frequencies for missing data items will not be presented.

#### 8.10.2.2 Overall Survival (OS)

The number of deaths will be summarised. The number of censored patients, and reason for censoring, will also be summarised.

OS will be summarised using the Kaplan-Meier technique. The quartiles (Q1, median, and Q3) of OS will be summarised, including 95% CIs. The percentage of patients survival rate at 3, 6, 9 and 12 months along with the 95% CI will be presented. The median (range) duration of follow-up among censored subjects (months) will also be presented.

### 8.11 Pharmacokinetics

For the definitions of handling, calculation and presentation of pharmacokinetic concentrations and parameters refer to Section 4.13. For PK parameters and calculations supporting Module 1, see section 7.2.2. There are no formal statistics planned for Module 1 PK results; these will be summarized descriptively by cohort, and sampling interval, or other appropriate subsetting.

Amount and cumulative amount of AZD4320 excreted will be listed and summarized by urine collection intervals per day of infusion during cycle 1, as appropriate. In addition, individual urine PK parameters will be listed.

### 8.12 Safety and Tolerability Evaluation

Safety, tolerability and DLT data will be listed and summarised as defined by the current AZ standards (oncology early phase study outputs).

Safety analysis set will be used for all safety and tolerability analyses. All listings and tables, other than those to assess DLTs during Cycle 1 in Part A, will be based on the safety analysis set. To describe the DLTs during Cycle 1 in Part A, the DLT-evaluable analysis set will be used.

Part A includes the AEs, AESIs, laboratory data, vital signs, ECG, LVEF (by MUGA/ MRI/ ECHO) as safety assessments. The listings and tables of all safety data for Part A will be created as described in this section. In addition, for Part A, DLTs will be listed and summarised; MTD (if determined) will be reported.

#### 8.12.1 Exposure and treatment administration

For the calculation and presentation of exposure and treatment administration refer to Section 4.14.1.

#### 8.12.2 Dose limiting toxicities (DLTs)

Refer to Section 4.14.2.

#### 8.12.3 Definition of Maximum Tolerated Dose and Definition of Recommended Phase II Dose

Refer to Section 4.14.3.

#### 8.12.4 Adverse Events

Refer to Section 4.14.4.

### 8.12.5 Deaths

Refer to Section 4.14.5.

### 8.12.6 Clinical Laboratory Evaluation

Refer to Section 4.14.6.

### 8.12.7 Vital Signs

Refer to Section 4.14.7.

### 8.12.8 ECGs

Refer to Section 4.14.8.

### 8.12.9 LVEF

Refer to Section 4.14.9.

### 8.12.10 Eastern Cooperative Oncology Group performance status (ECOG PS)

Refer to Section 4.14.10.

### 8.12.11 Tumour lysis syndrome (TLS)

Refer to Section 4.14.11.

## 8.13 Determination of Sample Size

#### 8.13.1.1 AZD0466 Monotherapy Escalation - Part A

The primary objective of Part A is to identify the MTD and RP2D of AZD0466 monotherapy. In Part A, 3 to 12 DLT-evaluable patients may be treated in each dose level using an mTPI-2 design (Guo et al 2017) permitting up to a maximum of 30 DLT-evaluable patients for dose exploration. In addition, any tolerated dose level may be expanded at the discretion of the sponsor in discussion with the SRC to include up to a total of 18 patients for further evaluation of PK, PD, safety, or biological efficacy. Up to a total of 58 patients will be enrolled to yield a maximum of 30 DLT-evaluable patients and 18 patients for further exploration in Part A. This limits the number of patients exposed to AZZ0466 consistent with the expected safety profiles of the study treatment, but includes sufficient patients to explore safety of the treatment, PK and effects on pharmacodynamic biomarkers, and to collect preliminary efficacy data.

## 8.14 Interim Analyses (Not applicable)

# 9 INTRODUCTION – Module 2

Module 2 will be initiated by the SRC (Appendix A5 of the study protocol) after a tolerated dose of AZD0466 has been determined in Module 1. This is a DDI study that will evaluate AZD0466 with voriconazole, a strong inhibitor of CYP3A4.

For further general study information refer to Section 1.

# 10 STUDY OBJECTIVES - Module 2

The core objectives and endpoints for the study are listed in Sections 2.1, 2.2 and 2.3; additional secondary endpoints for Module 2 are listed in Section 10.1

## 10.1 Secondary Objectives

| Objectives | Endpoints/Variables |
|---|---|
| To assess the drug-drug interaction potential between AZD0466 and the azole antifungal voriconazole. | AUC (AUC0-72 and AUClast) and $C_{max}$ of AZD4320 (total and released) after administration of AZD0466 alone and in combination with voriconazole |

# 11 INVESTIGATIONAL PLAN - Module 2

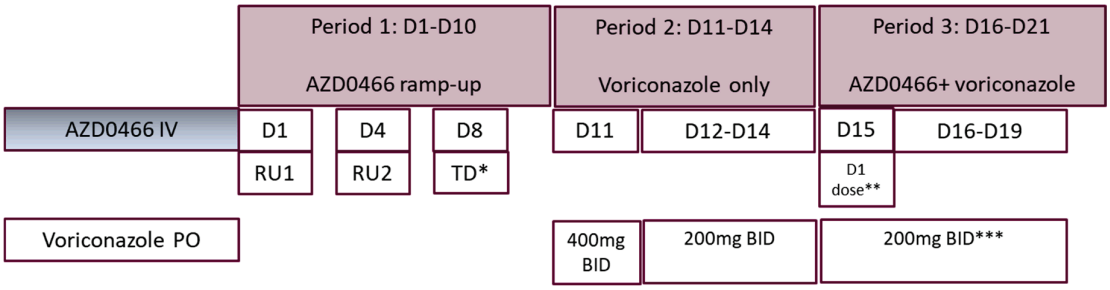
## 11.1 Overall Study Design

Module 2, a Phase I DDI study of AZD0466 and the azole antifungal agent voriconazole, will be conducted in patients with AML or ALL to determine the effect of voriconazole on the PK of AZD0466. This module will be conducted in selected sites in parallel with Module 1. During periods of parallel enrolment, patient entry into Module 1 will be prioritised at sites conducting both Module 1 and Module 2 of this protocol.

The schedule in Cycle 1 involves dose ramp-up in from a starting dose of AZD0466 on Day 1 (one quarter of the target dose), with subsequent titration to the intermediate dose on Day 4 (one half of the target dose), and to the target dose on Day 8. Patients will receive a loading dosage of oral voriconazole followed by maintenance dosing in Cycle 1, as specified in the prescribing information for voriconazole (Voriconazole Prescribing Information). The dose of AZD0466 administered in combination with voriconazole will be one quarter of the target dose, to mitigate against a potential increase in exposure to the active moiety AZD4320 if a DDI exists between AZD0466 and voriconazole.

A visual representation of the DDI component of Module 2 (Cycle 1) is shown in Figure 2.

**Figure 2 Schema for Cycle 1 of Module 2**




* The target dose (TD) of AZD0466 is the highest dose level determined as tolerated by the SRC in Part A of Module 1 at the point of first patient enrolment in Module 2.

**After reaching AZD0466 TD at D8 there will be a dose reduction on D15 to the D1 equivalent dose, with a return to full TD at the next AZD0466 administration day.

*** Voriconazole administration will be discontinued on Day 19 after collection of the last PK blood sample.

BID, twice a day; D, Day; IV, intravenous; PK, pharmacokinetic; PO, by mouth; RU1: first ramp-up dose; RU2: second ramp-up dose; SRC, Safety Review Committee; TD, target dose.

A minimum of 10 and up to 14 patients overall will be enrolled at selected sites to investigate the potential DDI between AZD0466 and voriconazole.

The DDI part of Module 2 (Cycle 1) will be performed in 3 periods over 21 days, as follows:

Period 1 (Days 1-10): AZD0466 infusion on Days 1, 4, and 8

Period 2 (Days 11-14): Voriconazole administration bid

Period 3 (Days 15-21): AZD0466 infusion (at the Day 1 equivalent dose) on Day 15 in combination with voriconazole bid on Days 15-19.

Module 2 Cycle 1 (DDI Part) will utilise a target dose of AZD0466 that has been declared tolerable in the dose escalation Part A of Module 1 (Table 22 in the study protocol). After reaching the target dose at Day 8, there will be a dose reduction at Day 15 to the Day 1 equivalent dose, and thereafter there will be a return to the full target dose.

In Module 2 Cycle 2 (after the DDI part), patients may receive AZD0466 as monotherapy at a higher target dose, if a new higher AZD0466 dose level was declared tolerable in Module 1. This dose increase may be implemented without a dose ramp up. This will allow patients to continue to receive study treatment at a tolerated dose within the predicted efficacious dose range in humans, see study protocol Section 11.1.3.1.

In Cycle 1, patients will be admitted as inpatients for 36 hours on Days 1-2, 4-5, 8-9, and overnight on Day 15. Additional inpatient admission days will be at the Investigator's discretion. During Period 2, voriconazole administration will occur on an outpatient basis.

The SoA for the DDI part (Cycle 1) of Module 2, including PK sampling times, is provided in Tables 21, 22 in the study protocol.

The SRC may assess safety data from Module 2 that could affect the conduct of Module 1.

## 11.2 Endpoints and Associated Variables

### 11.2.1 Efficacy Variables

For the definitions of the efficacy variables for the response evaluation criteria variables for ALL and AML, and extramedullary disease refer to the Section 3.2.1.

#### 11.2.1.1 Peripheral Blood

Peripheral blood will be collected for complete blood count (CBC) (laboratory safety assessment) as indicated in the SoA in Tables 21, 22 in the study protocol. CCI [redacted]

#### 11.2.1.2 Extramedullary Disease

Refer to Sections 3.2.1.2.

#### 11.2.1.3 Bone Marrow

Bone marrow core biopsy and bone marrow aspirate should be performed as specified in in the SoA

in Tables 25, 26 in the study protocol.

- Screening (between Day -28 and -1)
- Cycle 2 Day 16 or 17
- Cycle 3 and subsequent cycles between Day 23 to 28
- Disease progression or EoT visit

The disease progression sample collection may occur at the safety follow-up visit (if conducted in person) if not collected previously. Additional bone marrow or peripheral blood samples may be collected, as clinically indicated.

### 11.2.2 Pharmacokinetic Variables

Pharmacokinetic analysis of the plasma concentration data for total and released AZD4320 (and its metabolites (if available and appropriate)) when administered alone and in combination with voriconazole, when applicable, will be derived using non-compartmental methods in Phoenix® WinNonlin® Version 8.1 or higher (Certara); analysis will be performed by Covance on behalf of the sponsor.

PK analysis will, where data allow, be carried out using actual elapsed times determined from the PK sampling and dosing times in the database and following the schedule for plasma samples in Table 7.

**Table 7 Blood samples for plasma PK – Module 2**

| Study period | Day | Timepoint |
|---|---|---|
| Cycle 1 Period 1 | Day 1 | Pre-infusion |
| | | 30 minutes after the infusion the start of infusion (± 5 minutes) |
| | | End of the infusion (+10 minutes) |
| | | 2 hours from start of Day 1 infusion (± 15 min) |
| | | 6 hours from start of Day 1 infusion (± 30 min) |
| | | 9 hours from start of Day 1 infusion (± 1 hour) |
| | Day 2 | 24 hours after the start of the Day 1 infusion (± 2 hours) |
| | Day 3 | 48 hours after the start of the Day 1 infusion (± 3 hours) |
| | Day 4 | 72 hours after the start of the Day 1 infusion (up to 3 hours before infusion on Day 4) |
| | | End of the infusion on Day 4 (+10 minutes) |
| | Day 8 | Pre-infusion |
| | | End of the infusion (+10 minutes) |
| Cycle 1 Period 3 | Day 15 | Pre-infusion |
| | | 30 minutes after the infusion the start of infusion (± 5 minutes) |
| | | End of the infusion (+10 minutes) |

| Study period | Day | Timepoint |
|---|---|---|
| | | 2 hours from start of Day 15 infusion (± 15 min) |
| | | 6 hours from start of Day 15 infusion (± 30 min) |
| | | 9 hours from start of Day 15 infusion (± 1 hour) |
| | Day 16 | 24 hours after the start of the Day 15 infusion (± 2 hours) |
| | Day 17 | 48 hours after the start of the Day 15 infusion (± 3 hours) |
| | Day 18 | 72 hours after the start of the Day 15 infusion (± 3 hours) |
| | Day 19 | 96 hours after the start of the Day 15 infusion (± 3 hours) |
| Cycle 2 | Day 1 | Pre-infusion |
| | | End of the infusion (+10 minutes) |
| Cycle 3 and beyond | Day 1 | Pre-infusion |
| | | End of the infusion (+10 minutes) |

If actual elapsed times are missing, nominal times may be used, with approval by the Sponsor; if this occurs, it will be described in the report. 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 collected following doses administered on Cycle 1 Day 1 and Day 15.

**Plasma**

| | |
|---|---|
| $C_{max}$ | Maximum observed plasma (peak) drug concentration |
| $t_{max}$ | Time to reach peak or maximum observed concentration or response following drug administration |
| $\lambda z$ | Terminal rate constant, estimated by log-linear least squares regression of the terminal part of the concentration-time curve |
| $t_{1/2}\lambda z$ | Half-life associated with terminal slope ($\lambda z$) of a semi-logarithmic concentration-time curve |
| $AUC_{0-72}$ | 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 |

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

| | |
|---|---|
| $\lambda z$ lower | Lower (earlier) t used for $\lambda z$ determination |
| $\lambda z$ upper | Upper (later) t used for $\lambda z$ determination |
| $\lambda zN$ | Number of data points used for $\lambda z$ determination |

| | |
|---|---|
| λz lower | Lower (earlier) t 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) |
| λz span ratio | Time period over which λz was determined as ratio of $t_{1/2}$λz |

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 $\lambda_z$ 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 $\lambda_z$ will be discussed in CSR.

Additional PK parameters may be calculated as appropriate.

#### 11.2.3 Safety and Tolerability Variables

The primary objective is to assess the safety and tolerability of the AZD0466 in patients with advanced haematological malignancies.

As referenced in Section 3.2.3 the safety assessments performed will be:

- AE assessments,
- Clinical chemistry (including creatine phosphokinase) and haematology as described in Section 4.14.6,
- Amylase and lipase, coagulation indices, serum immunoglobulins, urinalysis, cardiac troponin and BNP (or NTproBNP), cortisol, ACTH and TSH parameters described in Section 4.14.6,
- Vital signs (SBP, DBP, pulse rate, oral body temperature), height and weight,
- 12-lead ECG,
- TLS (clinical and laboratory assessments),
- ECOG PS,
- Left ventricular ejection fraction (ECHO/MUGA).

The full list of laboratory measurements performed during the study that are used to evaluate safety and tolerability variables can be found in Table 1 and Table 2.

## 12 STATISTICAL METHODS - Module 2

### 12.1 Data Quality Assurance

Refer to Section 4.1.

### 12.2 General Presentation Considerations

Refer to the Section 4.2 for details of summary analyses. A clinical report will be produced from the database when all patients have had the opportunity to be treated and followed-up for 6 months.

### 12.3 General Variables

#### 12.3.1 Data cut-off

Refer to Section 4.3.1 for general considerations. For this module a clinical report will be produced when all patients have had the opportunity to be treated and followed-up for 6 months.

### 12.3.2 Study Day Definitions

Refer to Section 4.3.2.

### 12.3.3 Time Windows

Refer to Section 4.3.3.

### 12.3.4 Handling of Missing Data

Refer to Section 4.3.4.

### 12.3.5 Imputation Rules for Laboratory Values Outside of Quantification Range

Refer to Section 4.3.5.

## 12.4 Software

Refer to Section 4.4.

## 12.5 Analysis Sets

Details of the analysis sets are presented in Table 8.

**Table 8 Analysis Sets – Module 2**

| Population/Analysis set | Description |
|---|---|
| Safety | All patients who received at least one dose of AZD0466 |
| Intention-to-treat | All patients who received at least one dose of AZD0466 |
| Pharmacokinetics | Dosed patients with reportable plasma concentrations and no important AEs or protocol deviations that may affect PK |

A summary on which analysis set will be used for each outcome variable is provided in Table 9.

**Table 9 Summary of outcome variables and analysis sets – Module 2**

| Outcome variable | Analysis Set |
|---|---|
| ***Study Population/Demography Data*** | |
| Disposition | Enrolled |
| Demography and baseline characteristics | Safety |
| Important protocol deviations | Safety |
| Medical History | Safety |
| Prior/Concomitant Medication | Safety |
| ***Safety data*** | |
| Exposure | Safety |
| Adverse Events | Safety |
| Laboratory measurements | Safety |
| Vital Signs/ECG/Physical examination | Safety |
| ECOG PS | Safety |
| ***Efficacy Data*** | |
| Efficacy data listings | Intention-to-treat |
| ***Pharmacokinetics*** | |
| Pharmacokinetic variables | PK |

PK pharmacokinetic.

The number of enrolled patients included/excluded from each of the analysis sets will be summarised. Patients and data excluded from each analysis set will be listed with the reason for exclusion.

## 12.6 Study Patients

### 12.6.1 Disposition of Patients

Refer to Section 4.6.1.

### 12.6.2 Protocol Deviations

Refer to Section 4.6.2.

## 12.7 Demographics and Baseline Characteristics

Refer to Section 4.7.

## 12.8 Medical/Surgical History

Refer to Section 4.8.

## 12.9 Concomitant Medications and Other Treatments

Refer to Section 4.10.

## 12.10 Efficacy Evaluation

All of the collected response related data, such as from complete blood count (CBC), extramedullary disease status, bone marrow core biopsy and aspirate will be listed for all patients in the Intention-to-treat analysis set. Summaries will not be produced.

## 12.11 Pharmacokinetics

For the definitions of handling, calculation and presentation of pharmacokinetic concentrations and parameters refer to Section 4.13.

## 12.12 Safety and Tolerability Evaluation

Safety, tolerability data will be listed and summarized as defined by the current AZ standards (oncology early phase study outputs). Safety analysis set will be used for all safety and tolerability analyses. All listings and tables will be based on the safety analysis set

This include the AEs, AESIs, laboratory data, vital signs, and ECG as safety assessments.

Additional assessments will be included: ECHOs and serum immunoglobulins.

### 12.12.1 Exposure and treatment administration

For the calculation and presentation of exposure and treatment administration for AZD0466 refer to Section 4.14.1.

In addition, the exposure to voriconazole received will be listed for all patients. Actual and total treatment duration will be summarized by the following: mean, standard deviation, minimum, maximum, median and number of observations.

### 12.12.2 Adverse Events

Refer to Section 4.14.4.

### 12.12.3 Deaths

Refer to Section 4.14.5.

### 12.12.4 Clinical Laboratory Evaluation

Refer to Section 4.14.6.

### 12.12.5 Vital Signs

Refer to Section 4.14.7.

### 12.12.6 ECGs

Refer to Section 4.14.8.

### 12.12.7 Eastern Cooperative Oncology Group performance status (ECOG PS)

Refer to Section 4.14.10.

### 12.12.8 Tumour lysis syndrome (TLS)

Refer to Section 4.14.11.

### 12.13 Determination of Sample Size

The sample size of 14 patients has been determined empirically and is not based on statistical requirements. It is expected that the proposed sample size will provide sufficient data to evaluate the effect of voriconazole on exposure of AZD0466 (evaluated indirectly by AZD4320) while minimizing the number of patients exposed to study procedures.

### 12.14 Interim Analyses

No interim analysis is planned for this module.

## 13 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

As per the protocol, Section 11.7.6, analysis of efficacy data from Module 1 was to include data from Part B of Module 1. As Module 1 Part B was not initiated, and if data allow, the analyses described in Section 11.7.6 of the protocol will be applied to Module 1 Part A data.

## 14 REFERENCES

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