Clinical Study Protocol	
Study Intervention	AZD0466
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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

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

Protocol Number: D8241C00001

Amendment Number: 3

Study Treatment: AZD0466

Study Phase: Phase I/II

Short Title: A Phase I/II study of AZD0466 monotherapy or in combination in patients with advanced haematological malignancies

Acronym: NIMBLE

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	29 Sep 2022
Amendment 2	29 Mar 2022
Amendment 1	14 Jul 2021
Original Protocol	16 Dec 2020

Amendment 3 (29 September 2022)

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

Overall Rationale for the Amendment:

The global protocol was amended to: add a new dose escalation level to Part A of Module 1; to increase the number of patients permitted to be enrolled in Module 1 Part A; to increase the maximum feasible dose; to include response evaluation criteria for acute myeloid leukaemia (AML) for clinical trials; to include myelodysplastic syndrome (MDS) response evaluation criteria for neutrophil and platelet haematological improvement; and to address identified inconsistencies errors, typos, and to provide further clarification where needed. A summary of changes and the rationale for each change are tabulated below.

Section # and Name	Description of Changes	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis; 11.1.3.2 Part A Dose Escalation Scheme; 11.1.3.3 Dose Escalation, De-escalation, and Stopping Decision Rules; 11.7.2.1 AZD0466 Monotherapy Escalation – Part A	Increase in the number of patients allowed to be enrolled in Module 1 Part A from 40 to 48, hence increasing the number of DLT-evaluable patients from 30 to 36, the number of patients in Module 1 Part A from 58 to 66, in Module 1 from 146 to 154, and the total number of patients in the study from approximately 160 to 168.	A new higher dose level of AZD0466 (DL6) was added to the study design for Module 1 Part A. Consequently, the total number of patients in Module 1 Part A was increased based on the baseline assumption numbers needed per cohort plus a 25% fallout rate from disease progression.	Substantial
1.1 Synopsis; 11.1.3.2 Part A Dose Escalation Scheme; 11.1.3.3 Dose Escalation,	Amended language to read “approximately 36 DLT-evaluable patients”.	For consistency throughout the CSP.	Non-substantial

De-escalation, and Stopping Decision Rules; 11.7.2.1 AZD0466 Monotherapy Escalation – Part A			
1.2 Schema, Figure 1; 11.1.3 Rationale for Module 1, Figure 3	Updated to provide illustrative doses for DL4 and DL5 (in Figure 3), not exceeding a 2-fold increase of a dose declared tolerable by the SRC.	In line with FDA guidance on dose escalation for AZD0466 from study D8240C00003, the protocol for study D8241C00001 allowed up to a 2-fold dose increase at the discretion of the SRC. Based on emerging safety data for doses up to 1200 mg, this 2-fold increase was applied for dose escalation between DL1 to DL4 by the SRC. For dose escalation, illustrative doses are displayed that would not exceed a 2-fold increase of a dose declared tolerable by the SRC, or the maximum feasible dose as specified in Section 11.4.7.5.	Non-substantial
1.2 Schema, Figure 1; 11.1.3 Rationale for Module 1, Figure 3	Updated to reflect the addition of DL6, and to provide illustrative DL6 doses (in Figure 3).	A more gradual 50% increase is planned between DL4, DL5 and DL6. Dose level 6 will be determined by emerging safety data but is predicted to be a target dose of 5400 mg, though not exceeding 6000 mg, which is the maximum feasible dose as specified in Section 11.4.7.5. The purpose of including DL6 is to provide the option to explore a higher dose, given the predicted efficacious dose range of 600 to 6000 mg, based on pre-clinical studies, hereby balancing potential patient benefit against risk of possible toxicities.	Substantial
1.2 Schema, Figure 1; 11.1.3 Rationale for Module 1, Figure 3; 11.1.3.4 Dose Expansion Design; 11.3.1 Inclusion	Wording added and/or amended to clarify that patients included in Cohort B3 are ineligible for inclusion in Cohorts B1 and B2.	For clarity.	Non-substantial

Criteria			
1.2 Schema, Figure 1; 11.1.3 Rationale for Module 1, Figure 3; 12.1.5 Module 2 Study Design, Figure 4, Table 22; 12.4.1 Study Treatment(s) – AZD0466 and Voriconazole	Wording relating to the D15 dose in Period 3 of Module 2 has been amended to indicate that the dose of AZD0466 administered on D15 with voriconazole should be the same dose as the D1 dose, rather than ¼ of the target dose.	In order to assess the DDI (ie, change in AZD4320 exposures in the presence [D15] or absence [D1] of voriconazole), the D1 and D15 doses have to be the same. For the dose levels where there is a doubling of dose from D1 to D4 to D8, a quarter of the target dose at D15 is the same as D1. However, if the dose level at target (D8) is less than 4-fold higher than D1 (eg, DL5 and DL6) then the doses at D1 (first ramp up dose, in the absence of voriconazole) and D15 (quarter of the target dose, in the presence of voriconazole) will be different and therefore not allow DDI assessment (ie, not be able to differentiate the increase in AZD4320 exposures due to voriconazole versus increase in dose). Additionally, administering a dose greater than a quarter of the target dose on D15 may not allow for an adequate safety margin (of at least 4-fold, based on the anticipated magnitude of DDI with voriconazole) for co-administering AZD0466 with voriconazole, especially for DL6.	Non-substantial
2.1.2 Rationale for AZD0466 in treatment of haematological malignancies; 2.2 Benefit-Risk Assessment; 11.1.3.1 Justification for Starting Dose	Amended language relating to study D8240C00003 to reflect the fact that this study is no longer ongoing but has now closed.	To reflect the closure of study D8240C00003.	Non-substantial
2.3 Study Rationale; 5.1 Core Inclusion Criteria; 9.6 Efficacy; 11.1.3.2 Part A	“High-risk MDS” amended to “intermediate or higher risk MDS”.	Language amended to define more accurately the prognostic risk categories of patients eligible for enrolment.	Non-substantial

Dose Escalation Scheme; 11.2.3 Exploratory Objectives, Table 14; Appendix O 1 Prognostic Scoring System for MDS: The International Prognostic Scoring System – Revised (IPSS-R)			
5.1 Core Inclusion Criteria	Inclusion Criterion 9 amended to "White blood cell count must be < 10 x 10^9/L prior to the first dose in Cycle 1, Day 1. Treatment with hydroxyurea (AML) or high-dose steroids (ALL and leukaemia of ambiguous lineage) during screening and Cycle 1 to control white blood cell count is permitted.".	No change has been made to Inclusion Criterion 9. Text relating to permissible hydroxyurea and steroid usage has been updated for consistency throughout the protocol.	Non-substantial
6.6 Dose Modification and Toxicity Management, Table 4	Table 4 (Dose Reduction Modifications) updated.	To include all dosing options for dose modifications, based on proposed dose levels.	Non-substantial
6.6 Dose Modification and Toxicity Management, Table 4	Dose level 2 added to Table 4 and subsequent dose level numbering corrected.	To correct unintentional omission of dose level 2 from previous protocol version.	Non-substantial
8.7 Optional Genomics Initiative Sample; Appendix D 2 Genetic Research Plan and Procedures	Wording amended to reflect that the ICF for the optional genetic component of the study may form part of the main study ICF or be provided as an addendum to the main study ICF.	To reflect a change in process at some investigational sites.	Non-substantial
11.1.3.3 Dose Escalation, De-escalation, and Stopping Decision	Table updated to accommodate 6 dose levels.	Operating characteristics are based on the number of cohorts, therefore a re-run was required to allow the addition of DL6.	Substantial

Rules, Table 11			
11.4.7.5 Definition of Maximum Feasible Dose	Increase in the maximum dose permitted based on CMC quality specifications from 3600 mg to 6000 mg.	To align with the predicted efficacious dose range of 600-6000 mg per week and with emerging safety profile, CMC updated quality specifications accordingly.	Substantial
11.5.1 Schedule of Activities, Table 16	Timepoints for CT/MRI/PET scans (only if extramedullary disease) amended to align with Section 8.1.1.	Correction.	Non-substantial
11.5.1 Schedule of Activities, Table 16 and Table 17	Timepoints for plasma samples CCI [redacted] corrected to align with section 11.6.3.1.3.	Correction.	Non-substantial
11.5.1 Schedule of Activities, Table 16; 11.6.2.9.12 Overnight Stays for TLS Monitoring; 12.6.2.9.12 Overnight Stays for TLS Monitoring	Wording amended to "Overnight stays are recommended on …, but patients may be discharged prior to 36 hours post-dose, as per investigator discretion, if their TLS laboratory values are appropriate, and if the patient is able to return for a follow-up clinic visit to complete required safety and laboratory assessments within the specified time windows."	For clarity and consistency.	Non-substantial
11.5.1 Schedule of Activities, Table 16; 11.6.2.9.12 Overnight Stays for TLS Monitoring; 12.5.1 Schedule of Activities, Table 25 and 26; 12.6.2.9.12 Overnight Stays for TLS Monitoring	Wording in relation to TLS monitoring amended to: "At least twice in the first 24 hours after each administration of AZD0466, and as clinically indicated."	For clarity and consistency.	Non-substantial
12.1.5 Module 2 Study Design; 12.4.1 Study Treatments(s) –	Text amended and new Table 22 (Module 2 AZD0466 Dose Guidance) added.	To provide clarity on target doses and permissible change to a higher target dose based on SRC-declared	Substantial

AZD0466 and Voriconazole		tolerated dose in Module 1 Part A.	
12.5.1 Schedule of Activities, Table 25	Footnotes e to i corrected to match with the correct reference within the table.	Correction.	Non-substantial
12.5.1 Schedule of Activities, Table 25	Reference to Section 12.1.5 (Module 2 Study Design) added in relation to AZD0466 administration.	For clarity.	Non-substantial
Appendix F 1.1 Prophylaxis for TLS	Additional guidance added in relation to use of Rasburicase as prophylaxis.	Rasburicase is contraindicated for patients with G6PD deficiency. A recommendation to assess G6PD status was added for site support.	Non-substantial
Appendix F 1.1 Prophylaxis for TLS, Table 32; F 1.2 AZD0466 Dose Modifications for TLS, Table 33	Correction to references in table footnotes.	Correction.	Non-substantial
Appendix F 4 References	Howard et al 2011 added as a new reference.	Source information for prophylaxis for TLS and dose modifications for TLS.	Non-substantial
Appendix J Response Evaluation Criteria for Acute Myeloid Leukaemia	Addition of response criteria for clinical trials.	For information.	Non-substantial
Appendix K 1 References	Advani et al 2022 added as a new reference.	To support investigators in response assessment of ALL.	Non-substantial
Appendix O 1 Prognostic Scoring System for High-Risk MDS: The International Prognostic Scoring System – Revised (IPSS-R)	IPSS-R score of “bad” and very bad” amended to “poor” and “very poor” for the prognostic variable of cytogenetics. Prognostic factor score value 4.5 amended to 4.0. Bone Marrow blast % -	Correction to align with prognostic variables in “Revised international prognostic scoring system for myelodysplastic syndromes” in Greenberg et al 2012.	Non-substantial

	"> 10%" deleted from variable 4.		
Appendix P 2 Haematological Improvement (IWG 2018)	Response evaluation criteria for haematological improvement with respect to platelets and neutrophils added to table.	Updated in line with proposals for revised IWG 2018 haematological response criteria in patients with MDS included in clinical trials	Non-substantial

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CMC, Chemistry Manufacturing and Controls; D, day; DDI, drug-drug interaction; DL, dose level; FDA, Federal Food and Drug Administration; G6PD, Glucose-6-Phosphate-Dehydrogenase; ICF, informed consent form; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; MDS, myelodysplastic syndrome; SRC, Safety Review Committee; TLS, tumour lysis syndrome

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

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.

Short Title:

A Phase I/II Study of AZD0466 Monotherapy or in Combination in Patients with Advanced Haematological Malignancies

Rationale:

Proteins of the B-cell lymphoma 2 (Bcl-2) family regulate the intrinsic apoptosis pathway. Under normal conditions, apoptosis is prevented by pro-survival proteins (including Bcl-2 and B-cell lymphoma-extra large [Bcl-xL]) binding to and inhibiting the pro-apoptotic proteins (Bak and Bax). Overexpression of pro-survival Bcl-2 family proteins Bcl-2 and Bcl-xL has been associated with tumour initiation, progression, and resistance to a variety of current therapies (Czabotar et al 2014 and Delbridge and Strasser 2015).

AZD0466 is a drug-dendrimer conjugate that consists of an active moiety (AZD4320, a dual Bcl-2/Bcl-xL-specific inhibitor) covalently conjugated to a pegylated poly-L-lysine dendrimer, which gradually releases the active moiety by hydrolysis. AZD0466 exhibits potent Bcl-2/Bcl-xL-selective inhibition and has pharmacokinetic properties that minimise the potential for maximum concentration (C_{max})-dependent Bcl-xL-mediated adverse events (AEs).

AZD0466 has shown activity across a range of nonclinical models of haematological malignancy. This study is modular in design: the core protocol contains study information applicable to all patients in the study; Module 1 will evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of AZD0466 as monotherapy; Module 2 is a drug-drug interaction (DDI) study that will investigate the safety and establish the sensitivity of AZD0466 to strong inhibitors of cytochrome P450 3A (CYP3A) isoforms. Further modules may be added via protocol amendments to investigate AZD0466 in combination with other anticancer treatments. These additional modules will describe the rationale for each combination treatment arm, along with study information and assessments specific to the combination. Up to 4 additional modules may be added, where permissible by local regulations.

Objectives and Endpoints

The objectives and endpoints that are common to all study modules are listed below (Table 1).

See individual modules for the objectives and endpoints specific for each of the modules.

Table 1 Objectives and Endpoints

Objectives	Endpoints/Variables
Primary	
• To assess the safety and tolerability of AZD0466 in patients with advanced haematological malignancies	• Incidence of AEs and SAEs • Changes from baseline in laboratory findings, physical examinations, performance status, electrocardiograms, and vital signs
Secondary	
• 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
Exploratory	
• CCI	• CCI
• CCI • CCI	• CCI
• CCI	• CCI • CCI

AE, adverse event; CCI ; PK, pharmacokinetics; CCI CCI ; SAE, serious adverse event.

Overall Design

The study consists of individual modules, each evaluating the safety and tolerability of AZD0466 as monotherapy or with a specific combination treatment. The initial components are the core protocol, which contains information applicable to all modules, Module 1 (AZD0466 monotherapy), and Module 2 (DDI study of AZD0466 with voriconazole). Module 1 has 2 study parts: Part A consists of dose-escalation cohorts and Part B consists of expansion cohorts. A Safety Review Committee (SRC) (Appendix A 5) will review emerging data from evaluable patients in each cohort in Module 1 to monitor safety data on an ongoing

basis.

Disclosure Statement: This is a non-randomised, open-label, sequential, dose-escalation, and expansion study.

Number of Patients:

Approximately 168 patients will be assigned to study treatments across Modules 1 and 2. Additional patients may be recruited in response to emerging data that indicates a benefit to investigating alternative treatment regimens, combination agents, or indications through a protocol amendment.

- Module 1: AZD0466 monotherapy (n = 154 patients)

  Part A dose escalation cohorts:

  – In total, approximately 66 patients will be included in the dose escalation part. Up to 48 patients will be enrolled to yield approximately 36 dose-limiting toxicity (DLT)-evaluable patients. Cohorts may be expanded at the discretion of the SRC, by up to a maximum of 18 additional patients across all cohorts, for further evaluation of PK, pharmacodynamics (PD), safety, or biological efficacy.

  Initiation of Part B will depend on the evaluation of safety, tolerability, and PK in Part A.

  Part B dose expansion cohorts:

  – The dose expansion part of the study will enrol up to 88 patients. The decision for opening or closing Part B expansion cohorts and for starting new modules will be at the discretion of the sponsor in discussion with the SRC.

- Module 2: AZD0466 and voriconazole DDI study
  – Approximately 10 (maximum 14) patients will be assigned to study treatment in Module 2.

Additional patients may be recruited in subsequent modules in response to emerging data that indicates a benefit to investigating alternative treatment regimens, combination agents, or indications through a protocol amendment, where permissible by local regulations.

Treatment Groups and Duration:

All patients will receive AZD0466, and administration will continue until disease progression, initiation of alternative anticancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue study treatment.

Patients in Module 1 will receive AZD0466 monotherapy and patients in Module 2 will

receive AZD0466 monotherapy with and without voriconazole. Patients enrolled into subsequent modules incorporated via protocol amendments may receive AZD0466 in combination with other anticancer treatments.

Data Monitoring Committee:

There will be no data monitoring committee (DMC) for this study.

Safety Review Committee:

Refer to individual modules.

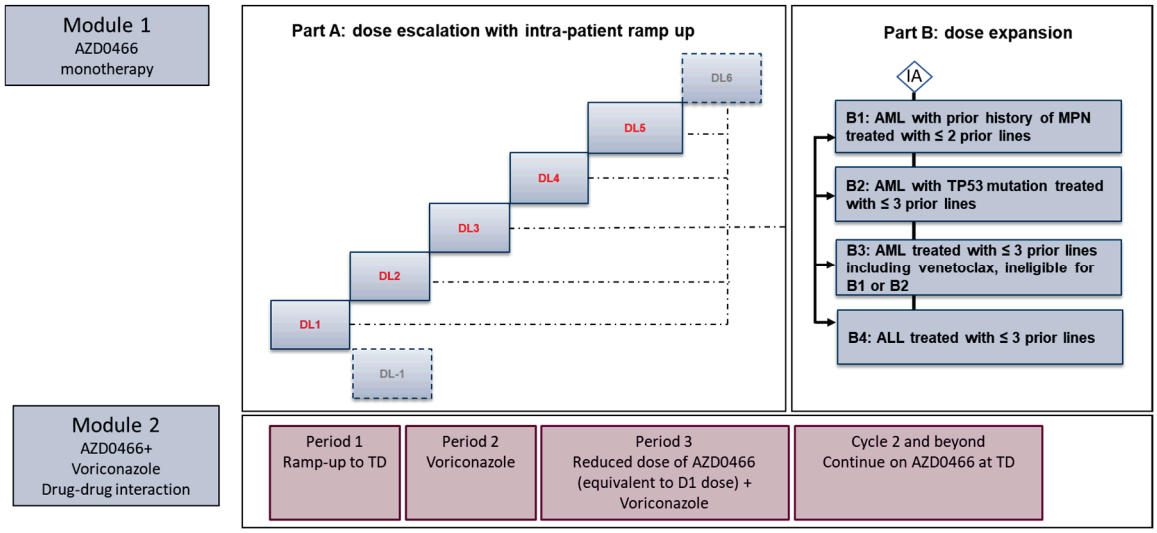
Statistical Methods:

Refer to individual modules for statistical considerations in this study.

1.2 Schema

The study design in summarised in Figure 1.

Figure 1 Study Schema



Dotted paths contingent on emerging data.
ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; D, Day; DL, dose level; IA, interim analysis; MPN, myeloproliferative neoplasm; TP53, gene encoding tumour protein p53; TD, target dose.

2 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 protocol contains study information applicable to all patients in this study. Further modules may be added via protocol amendment describing AZD0466 in combination with other treatments, where permissible by local regulations. A substantial protocol amendment with relevant supportive rationale will be submitted to the relevant authorities before starting a new module.

2.1 Background

2.1.1 Apoptosis and Cancer

Apoptosis is a cellular process necessary in the development and maintenance of tissue homeostasis. Dysregulation of apoptosis leads to a variety of pathologies, including cancer. The importance of apoptosis in regulating tumour growth was first identified in 1972 (

Kerr et al 1972) and evading apoptosis is considered one of the 6 hallmarks of cancer (Hanahan and Weinberg 2000).

Intrinsic, mitochondrial-mediated, apoptosis is regulated by members of the Bcl-2 family of proteins which can be divided into groups that interact to regulate the apoptotic pathway, as follows: 1) multi-domain, pro-survival proteins (eg, Bcl-2, Bcl-xL, Mcl-1, Bcl-2-A1, Bcl-w, and Bcl-B), 2) multi-domain pro-apoptotic proteins (eg, Bak and Bax), and 3) BH3-only pro-apoptotic proteins (eg, Bim, Noxa, Bad, Bid, and Puma). Under normal conditions, apoptosis is prevented by pro-survival proteins (including Bcl-2 and Bcl-xL) binding to and inhibiting the pro-apoptotic proteins. During cellular stress, such as deoxyribonucleic acid (DNA) damage, the apoptotic pathway is activated via sequestration of pro-survival proteins binding to BH3-only pro-apoptotic proteins (Czabotar et al 2014). However, overexpression of pro-survival proteins may deregulate this intricate balance, blocking apoptosis even under conditions of cell stress.

Bcl-2 family proteins were first shown to be critical in the regulation of apoptosis in cancer with the discovery of Bcl-2, and its identification as an oncogene in a follicular lymphoma cell line with a t(14;18) translocation that resulted in Bcl-2 overexpression (Vaux et al 1988). In addition, Bcl-2 has been associated with chronic lymphocytic leukaemia (CLL), diffuse large B-cell lymphoma (DLBCL), and neuroblastoma, while Bcl-xL overexpression has been reported in follicular lymphoma, DLBCL, multiple myeloma, and lung cancer (Adams et al 2018, Delbridge and Strasser 2015). Furthermore, progenitors of high-risk MDS were sensitive to agents that target not only Bcl-2 (Jilg et al 2016, Reidel et al 2018) but also Bcl-xL (Jilg et al 2016) The pro-survival Bcl-2 family proteins including Bcl-2 and Bcl-xL have been associated with tumour initiation, progression, and resistance to a variety of current anticancer therapies (Czabotar et al 2014 and Delbridge and Strasser 2015).

2.1.2 Rationale for AZD0466 in treatment of haematological malignancies

AZD0466 is a drug-dendrimer conjugate that consists of the active moiety, the dual Bcl-2/Bcl-xL-specific inhibitor AZD4320, covalently conjugated to a pegylated poly-L-lysine type dendrimer, which gradually releases the active moiety by hydrolysis. AZD0466 was developed to mitigate the nonclinical toxicity findings observed with AZD4320.

Administration of AZD0466 results in lower peak plasma levels of AZD4320 than can be readily achieved by direct infusion of AZD4320 at similar exposure concentrations. Thus, AZD0466 exhibits potent Bcl-2/Bcl-xL-selective inhibition and has PK properties that minimise the potential for C_{max}-dependent Bcl-xL-mediated AEs.

In vitro, AZD0466 induces apoptotic cell death in a variety of tumour cell lines, with particularly broad activity in cell lines derived from haematological malignancies. It also demonstrates significant dose-dependent in vivo anti-tumour activity as a single agent across a range of human tumour xenograft and patient-derived models, including acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), DLBCL, and small cell lung carcinoma. Enhanced nonclinical activity has also been observed for AZD0466 in combination with many standard-of-care anticancer therapies.

In nonclinical studies, anticipated on-target effects include rapid onset, transient abnormalities of hepatic transaminases, and thrombocytopenia. Based on nonclinical data, reduced QRS amplitude may also be observed at clinically predicted dose ranges. A detailed description of the chemistry, pharmacology, and nonclinical efficacy and safety of AZD0466 is provided in the Investigator's Brochure (IB).

AZD0466 has been administered to 9 patients with advanced solid malignancies at doses declared tolerable in the first-time-in-human study (D8240C00003). No dose-limiting toxicities (DLTs) have been recorded (data on file, AstraZeneca).

A detailed description of the chemistry, pharmacology, and nonclinical efficacy and safety of AZD0466 is provided in the IB.

2.2 Benefit-Risk Assessment

AZD0466 has dose-dependent in vivo anti-tumour activity as a single agent across a range of human tumour xenograft and patient-derived models, including haematological malignancies. Enhanced nonclinical activity has also been observed for AZD0466 in combination with many standard-of-care anticancer therapies.

Potential risks of AZD0466 may be anticipated due to its mechanism of action as a dual Bcl-2/Bcl-xL-specific inhibitor, published literature on clinical use of Bcl-2 and Bcl-2/Bcl-xL inhibitors, and observations from nonclinical studies of AZD0466 (drug-dendrimer conjugate)

and AZD4320 (active moiety). Important potential risks of AZD0466 include thrombocytopenia, hepatotoxicity, and QRS amplitude decrease. Potential risks of AZD0466 include tumour lysis syndrome (TLS), hypocellularity of the bone marrow and lymphoid tissue (neutropenia, lymphopenia, anaemia), thymus and spleen effects, pancreatic toxicity, DDIs, reproductive toxicity, and infusion site reactions. No safety findings emerged from the first-time-in-human study (D8240C00003) that would preclude investigation of AZD0466 in patients with advanced haematological malignancies.

The dosing schedule for AZD0466 utilises an intra-patient dose ramp-up schedule to mitigate the risk of TLS (Roberts et al 2016). The study protocol incorporates mandatory safety monitoring procedures, dose modification guidelines (Section 6.6), and additional guidance for management of specific AEs (Appendix F). The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable regulatory requirements.

The available nonclinical and clinical information supports an acceptable benefit-risk assessment for investigation of AZD0466 in patients with advanced haematological malignancies for which there are limited treatment options.

Additional considerations for the benefit-risk assessment of AZD0466 specific to individual modules are described in the respective modules.

2.3 Study Rationale

This study will investigate AZD0466 in patients with advanced haematological malignancies for which there are limited treatment options, including patients with intermediate and higher risk MDS. Patients with intermediate and higher risk MDS who are on a clinical continuum with AML have equally very poor prognosis and may also receive benefit from AZD0466 (Estey et al 2022, Greenberg et al 2012, Vardiman et al 2009).

The study is modular in design; the core protocol will contain study information applicable to all patients in this study. Module 1 will evaluate the safety, tolerability, PK, and efficacy of AZD0466 as monotherapy. Module 2 is a DDI study that will evaluate AZD0466 with voriconazole, a strong inhibitor of CYP3A4. The mechanism of action and nonclinical in vivo data suggest the potential to combine AZD0466 with a number of other anticancer treatments, resulting in enhanced activity. Further modules may be added via protocol amendment, where permissible by local regulations, and will include AZD0466 in combination with other anticancer treatments.

3 OBJECTIVES AND ENDPOINTS - CORE

The objectives and endpoints that are common to all study modules are shown in Table 2. See

individual modules for the objectives and endpoints specific for each of the modules.

Table 2 Objectives and Endpoints

Objectives	Endpoints/Variables
Primary	
• To assess the safety and tolerability of AZD0466 in patients with advanced haematological malignancies	• Incidence of AEs and SAEs • Changes from baseline in laboratory findings, physical examinations, performance status, electrocardiograms, and vital signs
Secondary	
• 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
Exploratory	
• CCI	• CCI
• CCI • CCI	• CCI
• CCI	• CCI • CCI

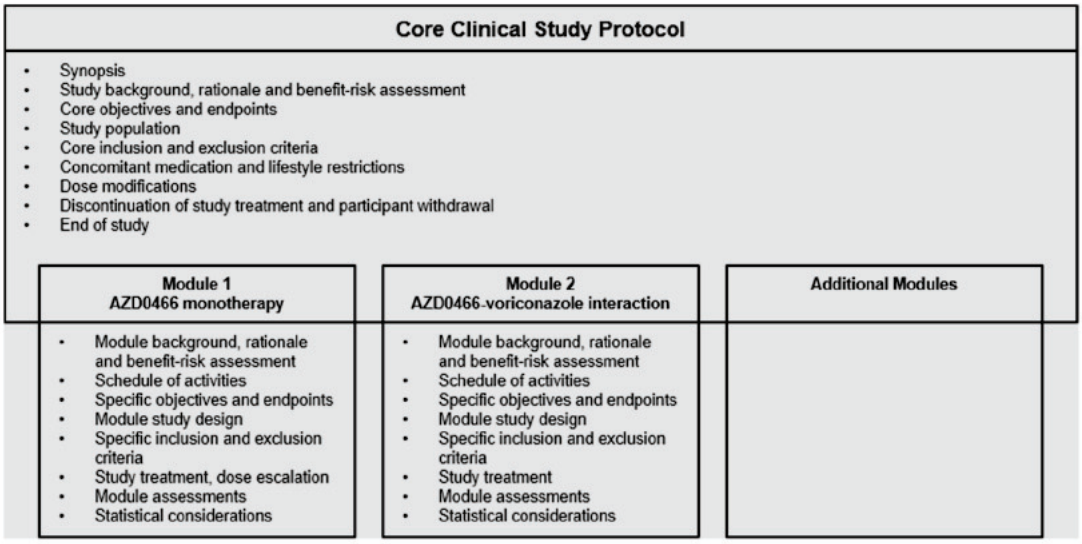
AE, adverse event; CCI ; PK, pharmacokinetics; CCI ; SAE, severe adverse event.

4 STUDY DESIGN - CORE

4.1 Overall 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. The initial protocol includes 2 modules; additional modules may be incorporated via regulatory amendments to the protocol together with any additional documents (eg, updates to quality and/or nonclinical information). Up to 4 additional modules may be added, where permissible by local regulations. The structure of this study protocol is shown in Figure 2; the core protocol contains elements common to all modules, and the individual modules contain the module-specific details relevant to that module.

Figure 2 Modular Protocol Design



As the mechanism of action of AZD0466 and in vivo data suggest that combining AZD0466 with other anticancer treatments may result in enhanced activity, it is anticipated that the study may evolve to incorporate additional modules to allow further evaluation of AZD0466 in defined populations or novel combinations. Emerging data from Module 1 (AZD0466 monotherapy) will guide the development of further modules to evaluate AZD0466 in novel combinations or defined patient populations, and findings from Module 2 will guide the use of concomitant medications in patients with advanced haematological malignancies. Hence, the modular study design will allow tailoring of study procedures and endpoints to specific treatment regimens and indications. The rationale for each module will be described in the respective module.

This study will characterise the PK profile of AZD0466 following intravenous (IV) administration (via PK profiles of the active moiety AZD4320 in plasma). Plasma concentrations and derived PK parameters for total and released AZD4320 will be determined and specified in each module.

As part of the clinical drug development program for AZD0466, AstraZeneca will investigate CCI [redacted] CCI [redacted] profiles and their relationship to drug effect. There are many potential benefits of this exploratory research, including identification of patients most likely to benefit from treatment, those who may not respond to treatment; and those who may experience adverse reactions. Ultimately, this research will provide the information and understanding required to deliver well tolerated and effective new medicines to patients.

4.2 Rationale for Study Design

The rationale for each module will be described in the respective modules.

4.2.1 Regulatory Amendments for Additional Modules

Additional modules will be provided as regulatory amendments to the protocol together with any additional documents (eg, updates to quality and/or nonclinical information, etc.) to the clinical trial application as required. Up to 4 additional modules may be added, where permissible by local regulations.

4.3 Justification for Dose

Refer to individual modules for details.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last patient in the study or last scheduled procedure shown in the Schedule of Activities (SoA) for the last patient in the study globally.

The End of Module is defined as the date of the last visit of the last patient in a Module or the last scheduled procedure shown in the respective SoA for the last patient in that Module.

A patient is considered to have completed the study if he/she has completed all phases of the study module including the last visit or the last scheduled procedure shown in the SoA including follow-up for overall survival (OS).

Patients may be withdrawn from the study if the study itself is stopped. The study may be stopped if, in the judgement of AstraZeneca, study patients are placed at undue risk because of clinically significant findings. The study may be terminated at individual centres if the study procedures are not being performed according to ICH GCP or if the recruitment rate does not

allow for completion of the study in the planned timeframe.

The results from each Module will be reported to regulatory authorities in accordance with clinical trial regulatory maintenance requirements in each region.

Following attainment of the final analyses for all modules and the overall end of study milestone, a final Clinical Study Report (CSR) including individual module reports and an assessment of fulfilment of the core clinical trial objectives will be produced for submission to Regulatory Authorities by the required timelines (ie, within 1 year of the overall end of the study).

4.5 Criteria for Stopping or Pausing Study Recruitment

AstraZeneca reserves the right to pause recruitment, temporarily suspend, or permanently terminate this study or components of the study at any time. AstraZeneca may at any point during the study pause enrolment if at least one of the following occurs:

- Fatal event deemed related to study intervention by the Sponsor and in discussion with the SRC after full aetiological work-up. This will also result in a comprehensive review of safety.
- Unexpected and life-threatening events deemed related to study treatment by the Sponsor and in discussion with the SRC.
- Sponsor decision that study patients are placed at undue safety risk (also see Section 4.4).
- Sponsor decision to discontinue the development of the study treatment in the proposed indications.

During Part A of Module 1 and during Module 2, AstraZeneca pharmacovigilance process and the SRC will evaluate toxicities study-wide (including evaluation of previous doses).

During Part B of Module 1, AZD0466 monotherapy dose expansion, a safety analysis will be performed at the time of the first interim analysis (IA) in each cohort. The study recruitment may be paused, pending investigation by the Sponsor and in discussion with SRC, if > 30% of patients experience AEs leading to study treatment discontinuation (see Section 11.7.9), the SRC may decide to stop the study, modify the study, or continue the study, based on the overall risk benefit of the agent. In addition, individual cohort level stopping criteria are provided in Section 11.7.2.2. Throughout the expansions, the AstraZeneca safety team and the SRC, will regularly review cumulative safety data including, but not limited to, toxicities that meet the DLT criteria.

5 STUDY POPULATION - CORE

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

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study at the time of starting study treatment. Under no circumstances can there be exceptions to this rule.

5.1 Core Inclusion Criteria

The inclusion criteria that are applicable to all modules in the study are described in this section. Additional module-specific criteria are included in the specific modules. If specific module criteria are more stringent than the core inclusion criteria, the module criteria must be met.

Informed Consent

1 Provision of signed and dated written informed consent prior to any study-specific procedures, sampling, and analyses. Informed consent is described in Appendix A 3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

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

Age

2 Patient must be aged ≥ 18 years, at the time of signing the informed consent. In some countries parental consent may be required in addition to an assent form for patients who are18 years of age.

Patient and Disease Characteristics

3 Diagnosis of AML, ALL, or intermediate or higher risk myelodysplastic syndrome (MDS; Part A only), which is histologically proven based on criteria established by the World Health Organization (WHO) as documented by medical records.

4 Patients must have received at least one prior line of therapy, and an established standard of care with proven benefit, and for which the patient is eligible, must not be available at the time of enrolment.

5 For AML or ALL patients, documented active disease requiring treatment that is relapsed or refractory defined as:

- Recurrence/relapse of disease after response to prior line(s) of therapy
- Progressive disease (refractory) on/after completion of the treatment regimen preceding entry into the study

6 For intermediate and higher risk MDS, documented active disease is defined as:
   – Patients with > 10% blasts, and/or
   – MDS with intermediate, high, or very high risk (risk score > 3) per the Revised International Prognosis Scoring System (IPSS-R) (Appendix O).

7 Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. Performance status must not have deteriorated by ≥ 2 levels within 2 weeks after providing informed consent.

8 Predicted life expectancy ≥ 8 weeks.

9 White blood cell count must be < 10 x 10^9/L prior to the first dose in Cycle 1, Day 1. Treatment with hydroxyurea (AML) or high-dose steroids (ALL and leukaemia of ambiguous lineage) during screening and Cycle 1 to control white blood cell count is permitted. Both medications can be started or stopped at any point during this period.

10 Adequate organ function at screening defined in Table 3:

Table 3 Organ Function Parameters

Category	Parameter	Value
Hepatic	Total bilirubin	≤ 1.5 × ULN
		≤ 3 × ULN in presence of Gilbert's syndrome
	AST and ALT	≤ 2.5 × ULN
Coagulation	INR	< 1.5 × ULN
Pancreatic	Lipase	≤ 1.5 × ULN
	Amylase	≤ 1.5 × ULN and absence of clinical pancreatitis
Renal*	Serum creatinine	≤ 1.5 × ULN
	CrCl by Cockcroft and Gault method: CrCl (mL/min) = (140 - age [years]) × weight (kg) × (F) [a] (72 × serum creatinine mg/dL) [a]where F = 0.85 for females and F = 1 for males	≥ 50 mL/min

*For patients with below ideal body weight, the 24-hour urine test may be used: ideal body weight (kg) = constant + 0.91 (height [cm] - 152.4); constant is 50 for men and 45.5 for women.
ALT, alanine transaminase; AST, aspartate transaminase; CrCl, creatinine clearance; INR, international normalised ratio; ULN, upper limit normal.

11 Adequate cardiac function as demonstrated by left ventricular ejection fraction (LVEF) > 50% on screening cardiac multigated acquisition (MUGA), magnetic resonance imaging (MRI), or echocardiogram (ECHO).

12 Willing and able to participate in all required study evaluations and procedures including receiving IV administration of study treatment and admission to the hospital, when required, for administration of study treatment and monitoring.

13 All patients must consent to and undergo both pretreatment and on-treatment fresh bone marrow aspirates and biopsies

14 For inclusion in the genetic component of the study, patients must fulfil the following additional criteria:

- Provision of signed, written, and dated informed consent for genetic research. If a patient declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this protocol, as long as they consented to the main study.

Reproduction

Women of childbearing potential must be willing to use highly effective contraceptive measures (see Section 5.3), should not be breastfeeding and must have a negative pregnancy test (serum) prior to start of dosing, or must have evidence of non-childbearing potential by fulfilling one of the following criteria at screening:

15 Women under 50 years of age would be considered postmenopausal if they have been amenorrhoeic for the last 12 months following the cessation of exogenous hormonal treatments and have serum follicle-stimulating hormone and luteinising hormone levels in the postmenopausal range for the institution.

16 Women with documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

Men should be willing to use barrier contraception (ie, condoms) and refrain from sperm donation during and after the conduct of the trial (see Section 5.3). If not done previously, storage of sperm before receiving AZD0466 will be advised to male patients with a desire to have children.

5.2 Core Exclusion Criteria

The exclusion criteria that are applicable to all modules in the study are described in this section. Please refer to the individual modules for additional module-specific exclusion criteria.

Patients must not enter the study if any of the following criteria are fulfilled:

Medical Conditions

1 Unresolved toxicity from prior anticancer therapy of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 2. Patients with Grade 2 neuropathy or Grade 2 alopecia are eligible.

2 Active idiopathic thrombocytopenic purpura.

3 Haemopoietic stem cell transplant < 100 days prior to the first dose of study treatment.

4 Immunosuppression for graft versus host disease (GVHD) or GVHD prophylaxis within 4 weeks prior to the first dose of study treatment. The following are **permitted**:

   (a) topical steroids for GVHD may continue indefinitely

   (b) systemic steroids for GVHD up to 2 weeks prior to the first dose of study treatment

   (c) Treatment with high-dose steroids (ALL and leukaemia of ambiguous lineage) for white blood cell count control is permitted during screening, and in Cycle 1 up to 4 days (maximum dexamethasone IV 40 mg/day or equivalent). It can be started or stopped at any point during this period.

5 Active central nervous system (CNS) leukaemia/leptomeningeal disease/spinal cord compression. Patients who have a history of CNS leukaemia must be free of CNS leukaemia for > 30 days prior to the first dose of study treatment, and the most recent 2 lumbar punctures must be negative for leukaemic cells, to be eligible.

6 Known history of infection with human immunodeficiency virus (HIV).

7 Known serologic status reflecting active hepatitis B or C infection.

   (a) Patients who are anti-HBc antibody positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR) result before enrolment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive will be excluded.

   (b) Patients who are hepatitis C antibody positive will need to have a negative PCR result before enrolment. Those who are hepatitis C PCR positive will be excluded.

8 Known uncontrolled infection with cytomegalovirus (CMV).

9 Patients should be tested for COVID-19 and those with active infection detected either using molecular or antigen tests in accordance with local testing guidelines will be excluded. Please note: Fully recovered patients (defined as no ongoing COVID-19 symptoms, except loss of sense of smell/taste) who present persistence of positive PCR test with a negative antigen test and the presence of IgG antibodies, may be included in the study.

10 As judged by the Investigator:

   – Any evidence of severe or uncontrolled systemic diseases, (eg, severe hepatic impairment, interstitial lung disease [bilateral, diffuse, parenchymal lung disease])

- Current unstable or uncompensated respiratory or cardiac conditions
- Uncontrolled hypertension
- History of, or active, bleeding diatheses (eg, haemophilia or von Willebrand disease)
- Uncontrolled active systemic fungal, bacterial, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).

11 Any of the following cardiac criteria:

- Patients with history of myocarditis within one year of study entry, or heart failure New York Heart Association Functional Classification Class 3 or 4 (Appendix N).
- Mean resting corrected QT interval (QTcF) ≥ 470 msec obtained from 3 electrocardiograms (ECGs), in the absence of a cardiac pacemaker.
- Abnormalities in rhythm, conduction or morphology of resting ECG that pose an unacceptable risk to the subject in the opinion of the enrolling physician.
- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age.

12 History of another life-threatening malignancy ≤ 2 years prior to first dose of study treatment. The following are **permitted**:

- Myelodysplastic syndrome or myeloproliferative neoplasm (including chronic myelomonocytic leukaemia [CMML]).
- Malignancy treated with curative intent and with no evidence of active disease present for more than 2 years before screening and considered to be at low risk of recurrence by the treating physician.
- Adequately treated lentigo malignant melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer.
- Adequately treated carcinoma in situ without current evidence of disease.

13 Any of the following procedures or any of the following conditions currently or in the 6 months prior to the first dose of study treatment:

- coronary artery bypass graft
- angioplasty
- vascular stent
- myocardial infarction
- angina pectoris
- haemorrhagic or thrombotic stroke, including transient ischaemic attacks or any other CNS bleeding.

Prior/Concomitant Therapy

14 Treatment with any of the following:

- Radiotherapy less than 3 weeks prior to the first dose of study treatment.
- Anticancer agents within ≤ 14 days or 5 half-lives (whichever is shorter) prior to the first dose of study treatment. Some anticancer agents may be strong CYP3A inducers or inhibitors, and should be withheld accordingly (Section 6.5.2).
- Treatment with high-dose steroids (ALL and leukaemia of ambiguous lineage) for white blood cell count control is permitted during screening, and in Cycle 1 up to 4 days (maximum dexamethasone IV 40 mg/day or equivalent). It can be started or stopped at any point during this period.
- Patients can continue to receive hydroxyurea (AML) until the start of Cycle 2 for white blood cell count control. It can be started or stopped at any point during this period.
- Patients who relapse while on maintenance-type ALL therapy or are receiving maintenance therapy for disease stabilisation should have therapy discontinued at least 7 days prior to first dose of study treatment.
- Immunotherapies and cellular therapies such as chimeric antigen receptor T cell therapy (CAR-T) within 4 weeks prior to the first dose of study treatment.
- Investigational drugs within ≤ 14 days or 5 half-lives (whichever is shorter) prior to the first dose of study treatment.
- Major surgery (excluding placement of vascular access) ≤ 21 days, or minor surgical procedures ≤ 7 days, prior to the first dose of study treatment. No waiting is required following implantable port or catheter placement.
- Prescription or non-prescription drugs or other products known to be sensitive substrates of BCRP, OCT2, OAT3, OATP1B1, OATP1B3, CYP2B6, CYP2C8, CYP2C9, or CYP2D6 (Section 6.5.2), which cannot be discontinued within 5 half-lives prior to the first dose of study treatment and withheld throughout the study until 14 days after the last dose of AZD0466.
- Reversible CYP3A inhibitors (Section 6.5.2), which cannot be discontinued within 14 days or 5 half-lives, whichever is shorter, prior to the first dose of study treatment and withheld throughout the study until 14 days after the last dose of AZD0466.
- Moderate or strong mechanism-based inhibitors or inducers of CYP3A4 which cannot be discontinued within 14 days prior to the first dose of study treatment, and withheld until 14 days after the last dose of AZD0466 (see Section 6.5.2 for a list of medications).
- Concurrent anti-coagulation therapy, including aspirin and heparin, which cannot be stopped. Heparin for vascular line management is allowed.

– Medications with known risk of Torsades de Pointes (TdP; see Appendix H), which cannot be discontinued within 5 half-lives of the first dose of study treatment and withheld until 14 days after the last dose of AZD0466. Some of the medications listed as a possible risk of TdP may be allowed at the Investigator's discretion after approval by the Medical Monitor when the patient has unmet medical need to continue receiving prohibited medication(s), no suitable alternative treatments are available, and the benefit-risk ratio is acceptable in the Investigator's opinion.

Prior/Concurrent Clinical Study Experience

15 History of hypersensitivity to polyethylene glycol (PEG), PEGylated products or drugs with a similar chemical structure or class to AZD0466 or other BH3 mimetic.

Other exclusions

16 Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

17 Judgement by the Investigator or Medical Monitor that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

18 Lactating, breastfeeding, or positive pregnancy test for women of childbearing potential.

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

20 Persons who, due to an official directive or court order, have been accommodated in an institution, must be excluded from participation.

21 Persons who are dependents of the Sponsor, Investigator, or the study site are also to be excluded from participation.

5.3 Lifestyle Considerations

Refer to the individual modules for any possible lifestyle restrictions in addition to those listed below.

Restrictions

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

Female patients

1 Women of childbearing potential should use highly effective contraception from the time of screening until 6 months after discontinuing study treatment. Acceptable methods of contraception include abstinence, tubal ligation, tricycle combined oral or transdermal contraceptives, copper-banded intrauterine devices or vasectomised partner. It is not known whether AZD0466 has the capacity to induce hepatic enzymes in humans so

hormonal contraceptives should be combined with a barrier method of contraception. Refer to Appendix I for effective methods of contraception.

2 Female subjects must not breastfeed and must not donate or retrieve ova for their own use from screening to approximately 6 months after the last dose of study treatment.

Male patients

3 Male patients should be asked to avoid unprotected sex with women of childbearing potential from the time of screening until 6 months after the last dose of study treatment. Where there are effects on spermatogenesis, patients should avoid procreation and donating sperm for 6 months after the last dose of study treatment. If male patients wish to father children, they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

4 Male patients should use a condom during the trial, and for 35 days after the last dose of AZD0466, with all sexual partners to avoid potential exposure to drug from the semen. Refer to Appendix I for effective methods of contraception.

5.3.1 Meals and Dietary Restrictions

Patients should refrain from consumption of Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, or grapefruit hybrids, from 14 days before the first dose of study treatment until 14 days after the last dose of study treatment.

5.3.2 Caffeine, Alcohol, and Tobacco

Patients should refrain from consumption of red wine. There are no caffeine or tobacco restrictions.

5.4 Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened up to 2 times. Re-screened patients should be assigned the same patient number as for the initial screening. However, re-screening should be documented so that its effect on study results, if any, can be assessed. Unused samples will be destroyed.

The reason for study withdrawal for all patients who are screen failures should be recorded in the electronic case report form (eCRF).

6 STUDY INTERVENTION - CORE

6.1 Study Treatment(s) Administered

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

All patients will receive treatment with the investigational product AZD0466. The AZD0466 drug product is provided with a custom solvent. The custom solvent is supplied to reconstitute AZD0466 drug product and subsequently dilute to lower concentrations, if needed, for clinical dosing.

Dosing details for AZD0466 administered as monotherapy, or in combination with other treatments used in patients with advanced haematological malignancies, is included in the specific module and associated handling instructions; combination treatments may be included in additional modules (where permissible by local regulations) and alternate frequencies and schedules may be instigated in response to emerging safety, tolerability, or PK data introduced through protocol amendment.

Patients should be encouraged to maintain adequate oral hydration during treatment with AZD0466, as prophylaxis for TLS, as described in Appendix F.

6.2 Preparation/Handling/Storage/Accountability

Only patients enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

6.2.1 AZD0466 Preparation and Administration

'AZD0466 Powder for Concentrate for Solution for Infusion' and 'Solvent for AZD0466 Powder for Concentrate for Solution for Infusion' should be prepared and administered according to the handling instructions available at the study centres.

Preparation of the dosing solutions must take place under aseptic handling conditions. Preparation and dosing of AZD0466 should not take place at temperatures exceeding 25°C (refer to handling instructions for allowable excursions). Administration, including 1-hour (+10 minutes) infusion time, must be completed within 3 hours of initial reconstitution (ie, addition of custom solvent to the powder).

The in-use stability period is limited due to the stability of the reconstituted material. Close dialogue between the pharmacy and research staff will be required to ensure that the material

is administered as quickly as possible following reconstitution, and within the in-use period/conditions stipulated.

6.2.2 Storage

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment shipments received and any discrepancies are reported and resolved before use of the study treatment(s).

All study treatments should be kept in a secure place under appropriate storage conditions. For specific storage conditions refer to the product label.

6.2.3 Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The study personnel at the investigational site will account for all drugs dispensed and for appropriate destruction of drugs to AstraZeneca. Unused drugs should be destroyed according to local guidelines, and the certificate of delivery destruction should be signed. Destruction should not take place until approved by the responsible person at AstraZeneca. All study supplies and associated documentation will be regularly reviewed and verified by the site monitor before destruction.

Further guidance and information for the final disposition of unused study treatment is provided in the Pharmacy Manual.

6.3 Measures to Minimise Bias

This is an open-label, non-randomised study; no blinding is required. If an unscheduled assessment is performed and the patient has not progressed, provided the assessment was performed within the visit window, subsequent assessments should be performed at the scheduled visits. This schedule is to be followed to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

6.3.1 Methods for Assigning Treatment Groups

The actual treatment given to patients will be determined by the opened module/cohorts with the priority always to an open dose-escalation cohort. As not all modules/cohorts will be open at a given time, patients can only be allocated to open modules/cohorts. If only one module/cohort is open, treatment assignment can still occur.

When the study treatment is provided centrally by AstraZeneca, the Interactive Response Technology (IRT) will provide the kit identification number to be allocated to the patient at

the treatment allocation visit and subsequent treatment visits.

6.4 Study Treatment Compliance

The administration of all study treatments should be recorded in the appropriate sections of the eCRF. Any changes from the dosing schedule, dose reductions and dose discontinuations should be recorded in the eCRF. The reason should also be documented.

The study treatment Storage Manager is responsible for managing the study treatments from receipt by the study site until the destruction of unused study treatments.

Use of doses in excess of that specified in the protocol is considered to be an overdose. Overdose and procedures to be followed in the event of overdose are described in Section 8.4.

6.4.1 Treatment Compliance for AZD0466

AZD0466 is administered by IV infusion and patients will receive AZD0466 directly from the Investigator or designee, under medical supervision. The date and time of dose administration will be recorded in the source documents and in the eCRF. The dose of study treatment and patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

The Investigator or pharmacist must retain records of all study treatments administered at the site. The Medical Monitor will check these records to confirm compliance with the protocol administration schedule.

6.5 Concomitant Therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Permitted Concomitant Medications and Treatments

- Anti-emetics are permitted for the treatment of nausea and vomiting and may be administered prophylactically for recurrent events. Routine pre-medication with anti-emetics for all patients is not advised.

- Hydroxyurea (AML) is permitted to control white blood cell count < 10 x 10^9/L during screening until the start of Cycle 2. It can be started or stopped at any point during this period. With the exception of hydroxyurea, no other direct anti-leukaemia therapy is permitted once study treatment has begun. Detailed documentation of dose and frequency must be recorded in the eCRFs and medication diary.
- High-dose steroids (ALL and leukaemia of ambiguous lineage) is permitted to control white blood cell count < 10 x 10^9/L during screening and Cycle 1 up to 4 days (maximum dexamethasone IV 40 mg/day or equivalent). It can be started or stopped at any point during this period. Detailed documentation of dose and frequency must be recorded in the eCRFs and medication diary.
- Low dose prednisone (10 mg or less) or equivalent dose of alternative steroid
- Intrathecal CNS prophylaxis may be continued.
- Supportive care, blood transfusions, and other medications that are considered necessary for the patient's wellbeing may be given at the discretion of the Investigator.
- Patients already receiving erythropoietin at the time of screening for the study may continue to receive it, provided they have been receiving it for > 1 month at the time study treatment is started. Prophylactic erythropoietin should not be started before Cycle 2.
- Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) may be considered for prolonged neutropenia (> 7 days) and < 5% blast in bone marrow following discussion with the Medical Monitor (Appendix F). However, long-acting pegylated G-CSF (pegfilgrastim) or darbepoetin is not permitted.
- Patients may receive treatment with receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors and/or bisphosphonates for the treatment of osteopenia, as recommended according to practice guidelines.
- Allopurinol is mandatory prophylaxis for TLS, with dosing and schedule as per institutional guidelines. Rasburicase should be considered based on Appendix F and institutional guidelines.
- Diuretics should be used with care; prophylactic use should be considered only if patients have signs of volume overload.
- Patients with an implanted pacemaker at study entry are eligible at the Investigator's discretion.
- Acetaminophen (paracetamol) is restricted to 3 grams per day or the maximum dose approved locally (if < 3 g/day) during the study.
- Inactivated vaccines or protein/RNA immunogen vaccines, including Coronavirus disease 2019 (COVID-19) vaccines, following a benefit/risk evaluation for the individual patient

and in accordance with local rules and regulations, and the local vaccination guideline. COVID-19 vaccines should be administered at least 7 days prior to the first dose of AZD0466, where possible. Use of live attenuated vaccines (eg, Influenza vaccine delivered as nasal spray) is prohibited.

6.5.2 Prohibited Concomitant Medications and Treatments

AZD0466 is an investigational drug for which no data on in vivo interactions are currently available. In vitro data have shown that the principal CYP enzyme responsible for the Phase I metabolism of AZD0466 is CYP3A4. In addition, in vitro data suggests AZD0466 has the potential to cause drug interactions through inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2D6, OATP1B1, OATP1B3, OAT3, OCT2, and BCRP.

- Besides those specified in individual modules, other anticancer agents, investigational agents, and radiotherapy should not be given while the patient is receiving study treatment. Note: Hydroxyurea and high-dose steroids are not permitted during Cycle 2 or subsequent cycles to control white blood cell count in patients. Radiation therapy for palliative care to focal sites is allowed.
- Due to potential DDIs, the following medications should not be administered while the patient is receiving AZD0466, and in the 14 days after the completion of study treatment. In addition, each type of the following medications should not be given within the specified time prior to starting AZD0466 treatment:
- 14 days for the following medications:

Strong inducers of CYP3A	apalutamide, avasimibe, carbamazepine, enzalutamide, lumacaftor, mitotane, phenytoin, rifabutin, rifampin, rifapentine, St. John's wort, and ivosidenib.
Moderate inducers of CYP3A	bosentan, dabrafenib, efavirenz, etravirine, genistein, lersivirine, lesinurad, lopinavir, modafinil, nafcillin, phenobarbital, primidone, ritonavir, semagacestat, talviraline, telotristat ethyl, thioridazine, tipranavir, enasidenib, and midostaurin.
Mechanism-based strong inhibitors of CYP3A	boceprevir, cobicistat, conivaptan, ritonavir, grapefruit juice, itraconazole, ketoconazole, lopinavir, saquinavir, telaprevir, troleandomycin, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir, montelukast, pioglitazone, rosiglitazone, phenytoin, mibefradil, ribociclib, telithromycin, and midostaurin.
Mechanism-based moderate inhibitors of CYP3A	amprenavir, conivaptan, crizotinib, cyclosporine, erythromycin, imatinib, letermovir, nilotinib, tofisopam, and verapamil.

Note: This list is not comprehensive and other medications that fit into a similar category should also follow this guideline.

- 5 half-lives or 14 days, whichever is shorter, of each medication for the following medications:

Reversible strong inhibitors of CYP3A	danoprevir, elvitegravir, indinavir, paritaprevir (ombitasvir and/or dasabuvir), posaconazole, tipranavir, and voriconazole*.
Reversible moderate inhibitors of CYP3A	aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, darunavir, dronedarone, faldaprevir, fluconazole, fluvoxamine, isavuconazole, Magnolia vine (Schisandra sphenanthera), and netupitant
Substrates of CYP2B6	bupropion.
Substrates of CYP2C8	repaglinide.
Substrates of CYP2C9	celecoxib, glimepiride, tolbutamide, and warfarin
Substrates of CYP2D6	atomoxetine, desipramine, dextromethorphan, eliglustat, nebivolol, nortriptyline, perphenazine, tolterodine, venlafaxine, amitriptyline, encainide, imipramine, metoprolol, propafenone, propranolol, tramadol, and trimipramine.
Substrates of OATP1B1 and OATP1B3	asunaprevir, atorvastatin, bosentan, cerivastatin, danoprevir, docetaxel, fexofenadine, glyburide, nateglinide, paclitaxel, pitavastatin, pravastatin, repaglinide, rosuvastatin, and simvastatin acid.
Substrates of OAT3	adefovir, cefaclor, ceftizoxime, famotidine, furosemide, ganciclovir, methotrexate, oseltamivir carboxylate, and penicillin G.
Substrates of OCT2	dofetilide and metformin
Substrates of BCRP	rosuvastatin and sulfasalazine.

*Voriconazole may be administered as study treatment as described in the schedule of assessments during the drug-drug interaction part of Module 2.

Note: This list is not comprehensive and other medications that fit into a similar category should also follow this guideline.

6.6 Dose Modification and Toxicity Management

AZD0466 may be withheld and the dose reduced due to haematological or non-haematological toxicities. In general, no AZD0466 dose modification is required if a patient experiences a Grade 1 or Grade 2 AE. However, AZD0466 should be modified or discontinued when the AEs described in this section are observed whether during ramp-up or once target dose is reached. Modifications based on cardiac AEs are described in Section 6.6.5.

Acceptable dose modifications shown in Table 4 are applicable during ramp-up and once target dose is reached. A maximum of 3 dose modifications are acceptable, except for CTCAE Grade 3 or 4 haemorrhage and any intracranial haemorrhage or haematoma, of which only one event is allowed. Also see Table 5, Table 6, Table 7, and Table 8.

Table 4 Dose Reduction Modifications

Cohort level	AZD0466 dose	Dose reductions		
		1 lower dose	2 lower doses	3 lower doses
DL-1	37.5 mg	--	--	--
	75 mg	37.5 mg	--	--
	150 mg	75 mg	37.5 mg	--
DL1	75 mg	37.5 mg	--	--
	150 mg	75 mg	37.5 mg	--
	300 mg	150 mg	75 mg	37.5 mg
DL2	150 mg	75 mg	37.5 mg	--
	300 mg	150 mg	75 mg	37.5 mg
	600mg	300 mg	150 mg	75 mg
DL3	300 mg	150 mg	75 mg	37.5 mg
	600 mg	300 mg	150 mg	75 mg
	1200 mg	600 mg	300 mg	150 mg
DL4	600 mg	300 mg	150 mg	75 mg
	1200 mg	600 mg	300 mg	150 mg
	2400 mg	1200 mg	600 mg	300 mg
DL5 [a]	1200 mg	600 mg	300 mg	150 mg
	2400 mg	1200 mg	600 mg	300 mg
	3600 mg	2400 mg	1200 mg	600 mg
DL6 [a]	2400 mg	1200 mg	600 mg	300 mg
	3600 mg	2400 mg	1200 mg	600 mg
	5400 mg	3600 mg	2400 mg	1200 mg
DL6 – alternative ramp-up [b]	1400 mg	600 mg	300 mg	150 mg
	2800 mg	1200 mg	600 mg	300 mg
	5400 mg	3600 mg	2400 mg	1200 mg

[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 Section 11.4.7.5.
[b] SRC to determine ramp-up as well as target dose.
DL, dose level; SRC, Safety Review Committee

While on study, patients diagnosed with COVID-19 and are thought to be receiving clinical benefit as deemed by the investigator may continue to receive AZD0466; however, must pause treatment if they meet pause or discontinuation criteria for dose modifications based on haematological parameters (Section 6.6.1, neutropenia), or CTCAE Grade 2 or higher non-haematological toxicities (Section 6.6.3), which would include pneumonia or other infectious complications.

6.6.1 Dose Modifications Based on Haematological Parameters

Myelosuppression and cytopenias are expected outcomes of leukaemia treatment, hence the aim of these dose modification guidelines is to prevent cumulative bone marrow suppression. Dose modifications for haematological changes are not allowed in the first 35 days after starting AZD0466 during Cycle 1 but supportive care should be provided as clinically indicated.

If a patient experiences a clinically significant and/or **unacceptable haematological toxicity** (including a DLT) considered by the Investigator to be related to study treatment and not attributable to the disease (or to disease-related processes) under investigation, dosing in subsequent cycles will be withheld and may subsequently be restarted at **one lower dose** (equivalent to one dose reduction; Figure 3) and supportive therapy (Appendix F) administered as required. Recommended dose modifications for haematological toxicities associated with AZD0466 observed in patients with haematological malignancies are shown in Table 5.

Table 5 Recommended Dose Modifications for Haematological Toxicities

Toxicity Grade	Occurrence	Action
Grade 4 neutropenia, with or without fever or infection	Occurrence prior to achieving remission	Administer prophylactic or treatment anti-infectives and growth factor support as clinically indicated. In most instances, AZD0466 should not be interrupted due to neutropenias prior to achieving remission; however, Investigator judgment may be applied to determine the aetiology of neutropenias.
	Occurrences after achieving remission and lasting at least 7 days	Withhold AZD0466 until infection is resolved, and antibiotics no longer required (except prophylactic) and ANC $\geq 0.5 \times 10^9$/L.[a] Dosing should be discussed with Medical Monitor.
Presence of significant bleeding events with or without thrombocytopenia, such as: • Grade 3 or 4 haemorrhage • Any grade serious haemorrhage event • Any grade intracranial haemorrhage or haematoma	Any	Withhold AZD0466 Maintain platelets at $\geq 50 \times 10^9$/L until resolution of bleeding. Following discussion with Medical Monitor, if evidence of clinical benefit, may consider re-challenge at 2 dose levels below current dose.

Table 5 Recommended Dose Modifications for Haematological Toxicities

Toxicity Grade	Occurrence	Action
For any other bleeding events eg, petechiae, purpura, bleeding gums, epistaxis, etc	Any	Monitor platelets and action as above if thrombocytopenia ≥ Grade 3

[a] Recovery of ANC to ≥ 0.5 x 10^9/L only applicable for patients with ANC ≥ 0.5 x 10^9/L at baseline/screening. For other patients discuss with Medical Monitor.

ANC, absolute neutrophil count.

6.6.2 Retreatment Criteria

Administration of AZD0466 in subsequent cycles will be guided by presence of measurable disease and adequate haematopoiesis, as described below.

Criteria for holding administration of AZD0466

The haematological criteria for withholding AZD0466 are as follows (Table 6):

1 **Inadequate haematopoiesis** as demonstrated by lack of peripheral blood count recovery [absolute neutrophil count (ANC) < 0.5 × 10^9/L, and platelet count < 50 × 10^9/L] in the absence of active bone marrow leukaemia (marrow blasts < 5%).
   - Some patients with low blood counts (ANC < 0.5 × 10^9/L and platelet count < 50 × 10^9/L) may have an aplastic or hypoplastic marrow (< 10% cellularity on bone marrow core biopsy). In patients with an aplastic or hypoplastic marrow and high leukaemic burden (eg, 5% cellularity and 95% leukaemic blasts), or if the Investigator determines the hypocellularity is attributable to residual leukaemia and not AZD0466, continued administration of AZD0466 may be permitted after discussion with the Medical Monitor.
   - If AZD0466 is withheld due to cytopenias and bone marrow aplasia/hypoplasia (< 10% cellularity on core bone marrow core biopsy) in the absence of leukaemia (eg, 5% leukaemic blasts), the patient should be closely monitored for blood count recovery and a repeat bone marrow assessment should be considered at weekly intervals.

2 **Progressive disease** (Appendix J and Appendix K): permanently discontinue AZD0466 in the absence of clinical benefit after discussion with the Medical Monitor.

Criteria for administration/continuation of AZD0466

The next cycle of AZD0466 can proceed without delay if ANC > 0.5 x 10^9/L and platelets > 50 x 10^9/L (without platelet or growth factor support). For patients without peripheral blood count recovery, the next cycle can start if there is active leukaemia with 5% or higher blasts in the bone marrow.

Table 6 Treatment Criteria Based on Bone Marrow, ANC and Transfusion Independent Platelet Count in the Absence of Peripheral Blasts

Event	ANC (10^9/L)	Platelets (10^9/L)	Bone marrow	Action
Cycle 1	> 0.5	> 50	-	• Evaluate bone marrow disease but continue to next cycle irrespective of percentage of blasts (unless determined to have rapidly progressive disease and taken off study)
	< 0.5	< 50	< 5% blast and cellularity < 10%	• No count recovery at day 35 hold AZD0466 wait to see if recovery at Day 42. • If no recovery, repeat bone marrow at Day 42. • Blasts count < 5% and no count recovery this is prolonged myelosuppression and a DLT. **Discontinue AZD0466** • Blasts count ≥ 5% and no count recovery, either continue to Cycle 2 or discontinue due to lack of response after discussion with Medical Monitor
	< 0.5	< 50	> 5% blast	• If significant reduction of leukaemic burden and clinical benefit as assessed by the Investigator, discuss with the Medical Monitor and may continue to Cycle 2. • If lack of clinical response or benefit consider discontinuation from study.
Cycle 2 and beyond	> 0.5	> 50	< 5% blast and normal cellularity (> 10 %)	• Continue to next cycle
			<5% blast and bone marrow hypocellular (< 10% cellularity)	• Hold AZD0466 and monitor for count recovery and assess bone marrow weekly. Once adequate hemopoiesis met (> 20% cellularity) restart AZ0466. Consider restarting at **one lower dose** than the current dose.
	> 0.5	> 50	> 5% blast	• Continue to next cycle if the patient is deriving benefit in the opinion of the Investigator
	< 0.5	< 50	Aplastic/ Hypoplastic (< 10% cellularity) and < 5% blasts	• Hold and monitor for count recovery and assess bone marrow weekly. Once adequate hemopoiesis met (> 10% cellularity), restart AZ0466. Consider restarting at **one lower dose** than the current dose. • If hypocellularity is due to high leukaemic burden (95% blast) or if Investigator attributes hypocellularity to residual leukaemia, consider dosing after discussion with Medical Monitor

Table 6 Treatment Criteria Based on Bone Marrow, ANC and Transfusion Independent Platelet Count in the Absence of Peripheral Blasts

Event	ANC (10^9/L)	Platelets (10^9/L)	Bone marrow	Action
	< 0.5	< 50	> 5% blast	• Discuss with Medical Monitor consider discontinuation due to continued lack of response. Further cycles may be considered

ANC, absolute neutrophil count; DLT, dose-limiting toxicity.

Contact the Medical Monitor to discuss action with AZD0466 for any scenario not described above.

6.6.3 Dose Modifications for Non-haematological Toxicities

Dose modifications for non-haematological toxicities may occur at any time and the management are shown Table 7 toxicities are graded according to CTCAE version 5. Special considerations for TLS and specific AEs are included in Appendix F.

Dose modifications for changes in hepatic biochemistry are summarised in Section 6.6.4.

If a patient experiences a clinically significant and/or unacceptable non-haematological toxicity (including a DLT), considered by the Investigator to be related to study treatment, and not attributable to the disease (or to disease-related processes) under investigation, dosing will be withheld or the dose reduced and supportive therapy administered as required.

Table 7 Dose Modifications for Non-haematological Toxicities

Event	Occurrence	Action with AZD0466
Non-haematological Toxicities (except hepatic and cardiac changes, see Sections 6.6.4 and 6.6.5)		
CTCAE Grade 1 non-haematological toxicities	Any	None
CTCAE Grade 2 non-haematological toxicities	First occurrence	None
	Second and subsequent occurrences	• Withhold AZD0466 until resolution to CTCAE Grade ≤ 1 or baseline. Maximum dose hold 21 days. • Restart AZD0466 at **same dose level** if at target dose or dose escalate if at ramp-up. • For > 3 occurrences, consider restarting AZD0466 at **one lower dose level if at target or consider to discontinue if at ramp-up.**

Table 7 Dose Modifications for Non-haematological Toxicities

Event	Occurrence	Action with AZD0466
CTCAE Grade 3 non-haematological toxicities	First occurrence	• Withhold AZD0466 until resolution to CTCAE Grade ≤ 1 or baseline. • Supportive therapy should be given as per institutional guidelines. • If resolution occurs in ≤ 7 days, restart AZD0466 at the **same dose level if at target or dose escalate if at ramp-up**, after discussion with Medical Monitor. • If no resolution in ≤ 7 days, withhold AZD0466 for up to a total of 21 days. • If resolution occurs in > 7 days but ≤ 21 days, restart AZD0466. At **one lower dose level if at target or consider to discontinue if at ramp-up**. • Discontinue AZD0466 if no resolution to CTCAE Grade ≤ 1 in < 21 days
	Second and subsequent occurrences	• Withhold AZD0466 and provide supportive therapy as per institutional guidelines. • **Discontinue if at ramp-up.** • If at target and resolution occurs in ≤ 7 days: restart AZD0466 at **one lower dose** after discussion with Medical Monitor. • If no resolution in ≤ 7 days, withhold AZD0466 for up to a total of 21 days. • If resolution to CTCAE ≤ Grade 1 occurs within 21 days, discuss with Investigator and Medical Monitor to further dose reduce by **one dose level** from previous dose, and to continue treatment if the patient is deriving clinical benefit. • Discontinue AZD0466 if no resolution to CTCAE Grade ≤ 1 in ≤ 21 days.
CTCAE Grade 4 non-haematological toxicities	Any	• Discontinue AZD0466.

CTCAE, Common Terminology Criteria for Adverse Events (Version 5)

6.6.4 Dose Modifications for Hepatotoxicity

AZD0466 dosing should be modified if a patient with normal or abnormal baseline liver function experiences a clinically significant and/or unacceptable change in hepatic biochemistry (including a DLT) described in Table 8 that is considered by the Investigator to be related to study treatment and not attributable to the disease (or to disease-related processes) under investigation.

Table 8 Dose Modification for Hepatotoxicity

Event	Occurrence	Action with AZD0466
For patients with normal baseline liver function: ALT and/or AST > 5 × ULN and ≤ 8 × ULN without concomitant elevation in bilirubin, which return to baseline within 7 days OR For patients with abnormal baseline liver function: ALT and/or AST > 5 × baseline and ≤ 8 × baseline or ALT and/or AST >7 × ULN and ≤ 10 × ULN, (whichever is lower in × ULN), without concomitant elevation in bilirubin, which return to baseline levels within 7 days	First occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline. • Restart AZD0466 at **same dose level if at target or dose escalate if at ramp-up.**
	Second occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline. • Restart AZD0466 at **one lower dose if at target or consider to discontinue if at ramp-up.**
	Third occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline. • Discontinue if at ramp-up. • If at target dose: Restart AZD0466 at **one lower dose** than the current dose if all values resolve to baseline or Grade ≤ 1 within 7 days and there is clear evidence of clinical benefit. A Q2W schedule may be considered. • Discontinue AZD0466 if the above criteria are not met.
For patients with normal baseline liver function: ALT and/or AST > 8 × ULN and ≤ 20 × ULN without concomitant elevation in bilirubin, which return to baseline or Grade 1 levels within 14 days OR For patients with abnormal baseline liver function: ALT and/or AST > 8 × baseline and ≤ 20 × baseline or ALT and/or AST > 10 × ULN and ≤ 20 × ULN, (whichever is lower in x ULN), without concomitant elevation in bilirubin, which return to baseline or Grade 1 levels within 14 days	First occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline. • Consider to discontinue if at ramp-up. • If at target dose: Restart AZD0466 at **one lower dose** than the current dose.
	Second occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline. • Discontinue if at ramp-up and not previously stopped. • If at target dose: Restart AZD0466 at **one lower dose** than the current dose and consider Q2W dosing schedule.
	Third occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline. • Restart AZD0466 at **2 lower dose levels** than current dose and resume on a Q2W schedule, if all values resolve to baseline or CTCAE Grade ≤ 1 within 14 days and there is clear evidence of clinical benefit. • Discontinue AZD0466 if the above criteria are not met.

Table 8 Dose Modification for Hepatotoxicity

Event	Occurrence	Action with AZD0466
For patients with normal baseline liver function: ALT and/or AST ≥ 3 × ULN with concomitant elevation in bilirubin ≥ 2 × ULN OR For patients with abnormal baseline liver function: ALT and/or AST ≥ 3 × baseline with concomitant elevation in bilirubin ≥ 2 × baseline	Any occurrence	• Discontinue AZD0466, refer to Appendix E for process to follow in order to identify and appropriately report episodes of potential Hy's Law.
ALT and/or AST > 20 × ULN	Any occurrence	• Discontinue AZD0466.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, common terminology criteria for adverse events; ULN, upper limit of normal; Q2W, every 14 days

6.6.5 Cardiac findings

AZD0466 should be withheld if any of the following occur at any time during study treatment:

- Symptomatic tachycardia
- Symptomatic hypotension
- QTcF shortening by 60 milliseconds compared to baseline, or interval value < 340 milliseconds, confirmed on at least 2 separate ECGs recorded 5 minutes apart
- QTcF prolongation of >500 milliseconds or QTcF prolongation from baseline by 60 milliseconds, confirmed on at least 2 separate ECGs recorded 5 minutes apart
- Any other cardiac findings of CTCAE Grade ≥ 2 if considered by the Investigator to be clinically significant

AZD0466 should be permanently discontinued if a CTCAE ≥ Grade 3 cardiac AE of any duration occurs during study treatment, if considered by the Investigator to be related to study treatment.

Patients should be monitored closely including continuous ECG monitoring as clinically indicated (including for QTcF prolongations > 500 milliseconds) and until such a time as deemed safe to discontinue monitoring by medical review, with cardiologist input considered in the instance of abnormal ECG findings. AZD0466 may be restarted after resolution of

cardiac findings to the patient's baseline at the discretion of the Investigator and after discussion with the Medical Monitor.

6.6.6 Infusion-site reactions

As with other drugs administered intravenously, local infusion-site reactions (eg infusion pain, infusion-site reaction, skin irritation, or vein irritation) may occur. For CTCAE Grade ≥ 2 reactions, the infusion of AZD0466 should be stopped; if the patient recovers without issue, a full dose may be considered at the next scheduled infusion. For CTCAE Grade 1 or transient reactions with recovery within 15 minutes, AZD0466 infusion may be restarted if timings permit it to be completed within the 3-hour window of stability.

6.7 Dose-limiting Toxicity

Refer to Module 1 (Section 11.4.7).

6.7.1 Definition of Maximum Tolerated Dose

Maximum tolerated dose will be determined using the modified toxicity probability interval (mTPI-2) approach as described in Module 1 (Section 11.4.7.3)

6.7.2 Definition of Recommended Phase II Dose

Refer to Module 1 (Section 11.4.7.4).

6.7.3 Definition of Maximum Feasible Dose

Refer to Module 1 (Section 11.4.7.5).

6.7.4 Safety Review Committee

Refer to Appendix A 5.

6.8 Treatment After the End of Study

Patients are permitted to receive further therapy or may continue to receive study treatment following the end of the study if, in the opinion of the Investigator, they are continuing to receive benefit from treatment. After discontinuation of study treatment, the Investigator will be at liberty to define further the most appropriate anticancer treatment.

Subsequent anticancer treatment is expected to be initiated following the cancer recurrence or development of a new cancer. Information on subsequent anticancer therapies should be recorded on the clinical database.

7 DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL - CORE

7.1 Discontinuation of Study Treatment

Patients who permanently discontinue study treatment will continue to have follow-up assessments per the SoA. Patients will be permanently discontinued from study treatment if the following criteria are met:

- Patient decision. The patient is at any time free to discontinue study treatment, without prejudice to further treatment. A patient who discontinues study treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments.
- Investigator decision
- Occurrence of any AE that, in the opinion of the Investigator or AstraZeneca contraindicates further dosing
- Pregnancy or intent to become pregnant
- Patients incorrectly initiated on study treatment (Section 7.1.2)
- Severe noncompliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from study treatment (eg, refusal to adhere to scheduled visits)
- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Decision to modify the development plan of the drug
- Initiation of alternative anticancer therapy including another investigational agent
- Confirmed disease progression (Appendix J and Appendix K)
- Death

All patients who are discontinued from study treatment should complete protocol-specified procedures for discontinuation of study treatment and follow-up procedures. Discontinued patients will be followed for survival, either through direct contacts or by collecting public records (eg, death certificates) as allowed by local laws.

The end of treatment (EoT) visit should be performed as soon as the patient is permanently discontinued from study treatment. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

Patients may withdraw from any aspects of the optional exploratory research at any time,

without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study. Procedures for withdrawal from the exploratory research are outlined in Appendix C 2.

7.1.1 Procedures for Discontinuation of Study Treatment

Discontinuation of study treatment does not affect the patient's participation in the study. A patient who decides to discontinue the study treatment will always be asked about the reason(s) for discontinuation and the presence of any AE. The patient should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the patient does not agree to continue to attend study visits in person, where possible, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Patients who are permanently discontinued from further receipt of study treatment, regardless of the reason, will be identified as having permanently discontinued treatment, followed by entry into follow-up. Patients who have permanently discontinued from further receipt of study treatment will need to be recorded in the IRT.

All patients will be followed for survival until the end of the study. Survival information may be obtained via telephone contact with the patient, patient's family, or by contact with the patient's current physician. Patients who decline to return to the site for evaluations should be contacted by telephone, following the timing and procedures indicated in the SoA, as an alternative.

7.1.2 Procedures for Handling Patients who are Incorrectly Initiated on Study Treatment

Patients who do not meet the inclusion/exclusion criteria should not, under any circumstances, receive study treatment. There can be no exceptions to this rule.

Where patients that do not meet the inclusion/exclusion criteria are incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the Investigator should inform the AstraZeneca Medical Monitor immediately.

Any patient who is found to have failed to meet the selection criteria, but has started treatment, will be removed from the study following completion of safety follow-up activities. Every effort should be made to ensure ineligible patients complete all safety follow-up activities. The Medical Monitor is to ensure all such contacts are appropriately documented.

7.2 Patient Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request. A patient who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records). Patients may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons; this is expected to be uncommon.

If the patient is on study treatment, this will be discontinued and the patient will be withdrawn from the study at this time. An EoT visit should be conducted at the time of withdrawal from the study, if it has not already been performed.

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

Patients that are withdrawn from the study but are evaluable per the definition of DLT-evaluable (Section 11.7.3) will not be replaced. Patients who do not experience a DLT (Section 11.4.7) can be replaced if the patient withdraws before the end of the DLT window. Any patient that is withdrawn and is not evaluable will be replaced to ensure a minimum number of evaluable patients.

7.2.1 Procedures for Withdrawal from Study

Patients who withdraw from the study will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen by an Investigator and undergo the assessments and procedures scheduled for the post-study assessment. AEs should be followed up and study treatment should be returned by the patient.

7.3 Lost to Follow-up

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

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

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients enrolled in the study, including those who did not get study treatment. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the patient will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

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

8 STUDY ASSESSMENTS AND PROCEDURES - CORE

The study assessments listed in this section apply to all modules. Safety assessments specific to each module will be listed in the respective sections. Study procedures and their timing are summarised in the SoA of each individual module. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment. Adherence to the study requirements, including those specified in the SoA for each module, is essential and required for study conduct.

The maximum amount of blood collected from each patient during the first 28 days of treatment for research assessments is not anticipated to exceed 275 mL.

Enrolment and Screening

At enrolment, each potential patient will provide informed consent prior to starting any study-specific procedures (see Appendix A 3). Screening will take place for up to 28 days from the date of enrolment. Every effort should be made to minimise the time between treatment

assignment and dosing, preferably to within 14 days. Patients who fail to meet the eligibility criteria will be recorded as a “screen failure”. Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened up to 2 times. Each potential patient is assigned a unique patient number. If a patient withdraws from the study, then the patient number cannot be reused.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all core and module-specific eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. The common screening forms will be considered as core protocol in the electronic data capture (EDC) system.

Procedures conducted as part of the patient’s routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the appropriate time frame relative to the first dose of study treatment, as defined in the SoA.

Demographic data and other characteristics will be recorded and will include gender, race, and ethnicity according to local regulations. A standard medical history, medication history, and surgical history will be obtained during review of the selection criteria. This will include the date of initial diagnosis of the disease under study, disease assessment within 28 days prior to the first dose of AZD0466, prognostic indices/disease profiling (if available from local laboratory results) for each disease indication, and all prior anticancer treatments (including responses and duration of response) for the disease under study.

Disease assessments and other clinical data obtained as standard of care (SoC) prior to consent may be used for the study, provided the assessments fall within the protocol-specified period prior to the first dose of study treatment.

Follow-up Period

The EoT assessment will be performed at the time study treatment is permanently discontinued. In addition, patients should be followed up for 28 days after the last dose of study treatment for any new AEs, follow-up of existing AEs and other study assessments. Patients should also be asked about concomitant medications at this follow-up. Patients will continue to be followed until disease progression or withdrawal of consent. All patients should be followed monthly for survival after the last clinic visit until withdrawal of consent or end of study for the purpose of assessing survival status (see Section 7.1). Patients who achieve a complete remission (CR) or CR with incomplete haematological recovery (CR_i) should be followed for relapse of disease until death.

8.1 Efficacy Assessments

Disease assessments will be based on bone marrow biopsy and aspirate in conjunction with assessment of peripheral blood samples. Assessments will be performed according to the individual module SoA. Unscheduled disease assessments may be performed if clinically indicated.

8.1.1 Disease Assessment in Patients With Known or Suspected Extramedullary Disease

Baseline disease assessments for patients with known or suspected extramedullary disease will be conducted using radiological imaging (computerised tomography [CT] with contrast preferred or magnetic resonance image [MRI], or if applicable, also positron emission tomography [PET] CT scan) of the neck, chest, abdomen, and pelvis performed within 28 days before the first dose of study treatment. Scans will be repeated at times of disease assessment as described in the individual module SoA (ie, after Cycle 1 and 2 and subsequently as per modules) until resolution of extramedullary disease.

Extramedullary disease is classified as follows:

- Measurable extramedullary disease: lesions that can be accurately measured in 2 dimensions by CT or MRI.
- Non-measurable extramedullary disease: all other lesions (including unidimensional lesions, lesions too small to be considered measurable), pleural or pericardial effusion, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed or followed by imaging techniques, or disease documented by indirect evidence only (eg, laboratory values).

Up to 6 measurable extramedullary disease lesions that are clearly measurable in 2 perpendicular dimensions will be followed as target lesions for each patient (target lesions must be > 1.0 cm in the longest diameter). The selected sites of measurable disease should be representative of the patient's disease. In addition, selection of target lesions should be from disparate regions of the body when these areas are significantly involved. If additional non-measurable extramedullary disease lesions are present, they may be recorded as non-target lesions and followed throughout the study. For patients with hepatosplenomegaly at baseline, the cranio-caudal measurement of the spleen and the longest diameter of the liver will be assessed at screening and all subsequent response evaluations.

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

8.2 Safety Assessments

Refer to each module for details.

8.3 Adverse Events and Serious Adverse Events

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

The definitions of an AE or serious adverse event (SAE) can be found in Appendix B. Adverse events will be reported to the Investigator by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorised representative). The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs will be collected from time of signature of the informed consent form throughout the treatment period and including the follow-up period (28 days after the last dose of the study treatment). If an event that starts after the defined safety follow-up period noted above is considered to be due to a late-onset toxicity to study treatment, it should be reported as an AE or SAE as applicable.

All SAEs will be recorded and reported to AstraZeneca or its designee within 24 hours. The Investigator will submit any updated SAE data to AstraZeneca within 24 hours of it being available.

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

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

8.3.2 Follow-up of AEs and SAEs

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

Any AEs that are unresolved at the patient’s last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated (this may be beyond the 28 days after the last dose of study treatment), but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

The following variables will be collected for each AE:

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

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication
- Description of the SAE

The grading scales found in the revised National Cancer Institute (NCI) CTCAE v5.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE v5.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) website (http://ctep.cancer.gov).

8.3.3 Causality Collection

The Investigator should assess causal relationship between each study treatment (AZD0466 and combination treatment) and each AE, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the study treatment?’

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

relationship is implied as ‘yes’.

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

8.3.4 Adverse Events Based on Signs and Symptoms

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

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests, vital signs, and ECGs will be summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, DLT criteria, are the reason for discontinuation of study treatment, or are considered to be clinically relevant as judged by the Investigator (which may include but is not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, eg, dose modification).

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

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

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

8.3.6 Hy’s Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation

and occurrences of aspartate aminotransferase/transaminase (AST) or alanine aminotransferase/transaminase (ALT) ≥ 3 × upper limit of normal (ULN) together with total bilirubin (TBL) ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.7 Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the study treatment is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of > 5% leukaemic blasts in the bone marrow, appearance or increase of leukaemic blasts in peripheral blood, or development of extramedullary disease should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.3.8 Disease Under Study

Symptoms of disease under study (DUS) are those which might be expected to occur as a direct result of the advanced haematological malignancy. Events which are unequivocally due to DUS should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the study treatment.

8.3.9 New Cancers

The development of a new cancer should be regarded as an SAE and will generally meet at least the serious criteria of important medical event if no other criteria applies. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study.

8.3.10 Deaths

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

- Death, which is unequivocally due to disease progression, should be communicated to the Medical Monitor at the next monitoring visit and should be documented in the CRF module, but should not be reported as a SAE during the study.
- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the Medical Monitor as a Grade 5 SAE within 24 hours. It should also be documented in the CRF module. The SAE report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the CRF module. A postmortem may be helpful in the assessment of the

cause of death, and if performed, a copy of the postmortem results (with translation of essential details into English) should be reported in an expedited fashion to the sponsor representative within the usual timeframes.

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

8.3.11 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study treatment or to study procedures. All SAEs will be recorded in the eCRF.

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

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

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

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

If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes an SAE and is to be reported as such.

For further guidance on the definition of a SAE, see Appendix B of the CSP.

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

drug.

Where hospitalisation for longer than the mandated 24 hours is required it should be noted that if this is due to occurrence of an AE then the event must be reported as an SAE, per definition. However, if it is purely for the purposes of extended observation then this does not qualify as an SAE and does not need to be reported.

8.3.12 Adverse Events of Special Interest

An adverse event of special interest (AESI) is an AE, serious or non-serious, that is of scientific and medical interest specific to the understanding of the study treatment and may require closer monitoring, with collecting of additional information by the Investigator and reporting these to the sponsor. The rapid reporting of AESIs by the Investigator allows ongoing surveillance of these events in order to further characterise and understand them in relation to the use of the study treatment. All AESIs should be recorded in the eCRF as soon as possible, preferably within 24 hours. All AESIs that are also serious (ie, are SAEs) should be reported to AstraZeneca Patient Safety within 24 hours, as per safety reporting requirements.

In this study, the following are considered to be AESIs:

- Tumour lysis syndrome (Appendix G)
- 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

8.3.13 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca within 24 hours except for pregnancy that is discovered before the study patient has received any study treatment.

8.3.13.1 Maternal Exposure

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

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.11) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.3.13.2 Paternal Exposure

The outcome of any conception occurring from the date of the first dose until 6 months after the last dose of study treatment should be followed up and documented. Information on the pregnancy of a patient's partner must be obtained directly from the patient's partner. Therefore, prior to obtaining information on the pregnancy, the Investigator must obtain the consent of the patient's partner.

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose and for 35 days after the last dose of AZD0466 -plus 6 months - should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

If a pregnancy occurs in a patient's partner within the timeframe specified above, Investigators or other site personnel will inform the appropriate sponsor representative immediately, or no later than 24 hours of when he or she becomes aware of it.

The same timelines apply when outcome information is available. Detailed instructions on reporting pregnancies are provided in the Investigator manual separate from this protocol.

8.3.14 Medication Error

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up

Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.11) and **within 30 days** for all other medication errors.

The definition of a medication error can be found in Appendix B 4.

8.4 Overdose

For this study, any dose of AZD0466 greater than the highest dose intended for the individual patient at that timepoint in the protocol will be considered an overdose. For example, during ramp-up, doses exceeding the specified dose at that timepoint will also be classified as an overdose, even if the dose administered is less than the target dose for that patient.

Investigators should be advised that any patient who receives a higher dose of AZD0466 than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly. There are no data available on overdose with AZD0466 and there is no known antidote.

Overdose should be recorded as follows:

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.11) and **within 30 days** for all other overdoses.

Refer to the individual modules for overdose information on module-specific study treatments.

8.5 Human Biological Samples

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

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

PK samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.

PK samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.5.1 Pharmacokinetics

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

Samples for determination of AZD4320 concentrations in plasma (and/or urine) will be analysed by a suitable vendor on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

All samples still within the known stability of the analytes of interest at the time of receipt by the bioanalytical laboratory will be analysed.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

8.5.1.1 Collection of Pharmacokinetic Samples

Refer to each individual module for details of collection schedule and procedures for PK sample collection.

8.5.1.2 Determination of Drug Concentration

Refer to each individual module for details of determination of drug concentration.

8.5.2 Pharmacodynamics

Refer to each module for details of collection schedule and procedures for PD samples collection.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

Refer to individual modules for details on module-specific mandatory samples for biomarker analysis.

8.6.1.1 CCI

CCI [redacted]

8.6.2 Other Study Related Biomarker Research

Refer to individual modules for details.

8.7 Optional Genomics Initiative Sample

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

CCI [redacted]

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

For storage and destruction of genetic samples, see Appendix D. See Appendix C for labelling, chain of custody, shipment, handling and withdrawal of consent for donated biological samples.

8.8 Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS - CORE

9.1 Statistical Hypotheses

No formal statistical hypothesis testing is planned.

9.2 Sample Size Determination

Please refer to individual study modules for details of sample sizes.

9.3 Populations for Analysis

Please refer to individual study modules for details of populations for analysis.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints that will be applicable across all modules.

9.5 General Considerations

Descriptive statistics will be used for all variables. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total.

All data collected will be listed. Demographic data will be summarised on the safety population set. Exposure data will be summarised on the safety population set. The efficacy endpoints for response will be summarised on the appropriate evaluable for response population set. The efficacy endpoints for OS will be summarised on the intent-to-treat (ITT) population set (Section 11.7.3). Safety data will be summarised on the safety population set (Section 11.7.3).

Demographic data

Characteristics of the patients, including medical history and disease characteristics at baseline will be listed for each patient and summarised by dose group where appropriate. Reasons for discontinuation of study treatment will be listed including the study day of treatment discontinuation and will be summarised by dose group if appropriate.

Exposure

Exposure to study treatment ie, total amount of study drug received will be listed for all patients. Total exposure and total time on study (date of last dose minus date of first dose) will be summarised by the following: mean, standard deviation, minimum, maximum, median and

number of observations.

9.6 Efficacy

Clinical responses (including CR and CR_i will be listed and summarised by dose group and by appropriate response category for AML, ALL, and intermediate and higher risk MDS. Clinical responses for AML, ALL, and intermediate and higher risk MDS will be derived by applying the criteria as described in Appendix K, Appendix J, and Appendix P. In addition, bone marrow and [redacted] and changes from baseline scaled ratio will be summarised appropriately.

9.7 Safety

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs, and ECG changes. These will be collected for all patients.

All patients receiving a particular dose level within each part of the study will be grouped together for summary and analysis and defined as a dose group.

9.7.1 Adverse Events

All patients who receive at least one dose of AZD0466 will be included in the assessment of the safety profile (safety analysis set). At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

Data from all cycles of initial treatment will be combined in the presentation of safety data. AEs will be listed individually by patient and dose group. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group. The number of patients experiencing each AE will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade. The number and percentage of patients with AEs in different categories (eg, causally related, CTCAE grade ≥ 3, etc) will be summarised by dose group, and events in each category will be further summarised by MedDRA system organ class and preferred term, by dose group. SAEs will be summarised separately if a sufficient number occur.

Any AE occurring before the first dose of study treatment (ie, before study Day 1) will be included in the data listings but will not be included in the summary tables of AEs.

Any AE occurring within the defined 28 day follow-up period 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 after the 28 day follow-up period after discontinuation of study treatment will be listed separately, but not included in the summaries.

9.7.2 Other safety parameters

Haematology, clinical chemistry, vital signs, ECG data (including QTc as calculated by Fridericia's formulae), and concomitant medications will be listed individually by patient and summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum, and number of observations will be used. Details of any deaths will be listed for all patients.

Graphical presentations of safety data will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration, or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared to baseline.

9.8 Other Analyses

Please see individual modules for details.

9.9 Interim Analyses

Please see individual modules for details.

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11 MODULE 1: AZD0466 MONOTHERAPY DOSE ESCALATION (PART A) AND DOSE EXPANSION (PART B) IN PATIENTS WITH ADVANCED HAEMATOLOGICAL MALIGNANCIES

11.1 BACKGROUND - MODULE 1

11.1.1 Study Treatment

Study treatment in Module 1 is the investigational product, AZD0466. Refer to Section 6 and Section 11.4; further details are provided in the IB.

11.1.2 Nonclinical Information and Correlative Studies

Refer to Section 2.1.2; further details are provided in the IB.

11.1.3 Rationale for Module 1

The overall rationale for investigating AZD0466 in patients with advanced haematological malignancies is presented in Section 2.3.

As AZD0466 has not been investigated in patients with advanced haematological malignancies, Module 1 Part A is a dose escalation assessment of the safety and tolerability of AZD0466 to determine the recommended dose and schedule for further evaluation. Module 1 Part B will further explore the preliminary anticancer efficacy of AZD0466 in 4 cohorts of patients with AML or ALL (Table 9). These expansion cohorts have been proposed on the basis of preclinical data supporting potentially enhanced efficacy of AZD0466, a dual Bcl-2/Bcl-xL inhibitor, compared to compounds that inhibit Bcl-2 alone and in consideration of the unmet medical need in each of these populations.

A summary of the advanced haematological malignancies included in the Part B dose expansion cohorts is shown in Table 9.

Table 9 Summary of Disease Characteristics for Patients Enrolled in Module 1 Part B Dose Expansion Cohorts

Expansion cohort	Lineage	Prior history myeloproliferative neoplasm	*TP53* mutation	Prior treatment
B1	Acute myeloid leukaemia	Yes	Yes or No	≤ 2 lines venetoclax permitted
B2	Acute myeloid leukaemia	No	Yes	≤ 3 lines venetoclax permitted
B3	Acute myeloid leukaemia	No	No	≤ 3 lines; to include venetoclax
B4	Acute lymphoblastic leukaemia	-	-	≤ 3 lines

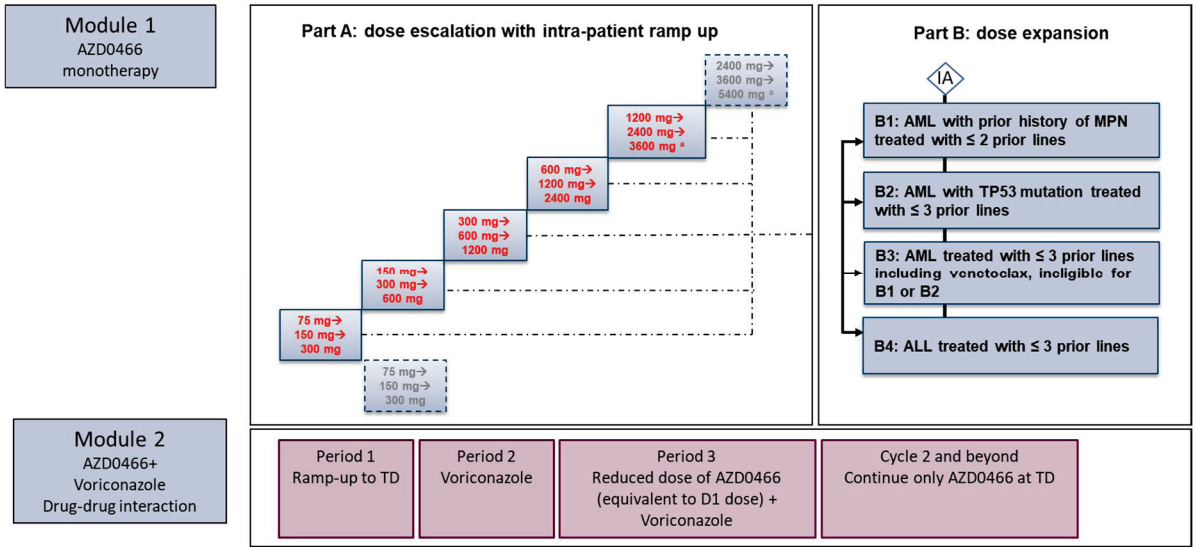
TP53, gene encoding tumour protein p53.

Design of Module 1

Module 1 Part A is a Phase I dose escalation evaluation of AZD0466 monotherapy; Module 1 Part B is a dose expansion evaluating the recommended Phase II dose of AZD0466 monotherapy in 4 cohorts of patients.

A visual representation of Module 1 is shown in Figure 3.

Figure 3 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 Section 11.4.7.5.

Dotted paths contingent on emerging data.

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; D, Day; IA, interim analysis; MPN, myeloproliferative neoplasm; SRC, Safety Review Committee; TD, target dose; TP53, gene encoding tumour protein p53.

11.1.3.1 Justification for Starting Dose

A physiologically based PK model validated across nonclinical species was used to predict AZD0466 human PK and, in conjunction with the PK/PD model used, to predict human doses and exposures expected to drive tumour regression. The efficacious dose range is predicted to be AZD0466 10 to 100 mg/kg per week, or 600–6000 mg per week administered as a one-hour IV infusion (based on a 60-kg patient). Further information on PK modelling of AZD0466 can be found in the IB.

Study D8240C00003 demonstrated that weekly administration of AZD0466 200 mg IV is tolerated in patients with advanced solid malignancies (data on file, AstraZeneca). The treatment schedule for patients with haematological malignancies included an intra-patient dose ramp-up, derived from the approach initially taken for venetoclax (a potent, selective inhibitor of Bcl-2) in patients with CLL (Cheson et al 2017, Davids et al 2017) and AML (DiNardo et al 2018, DiNardo et al 2019). The AZD0466 schedule involved dose ramp-up in

Cycle 1 from a starting dose on Day 1, with subsequent titration to the intermediate dose on Day 4, and to the target dose on Day 8, with weekly IV administration thereafter at the target dose.

Study D8240C00003, now closed, enrolled patients with advanced solid malignancies, who were dosed with 50, 100, or 200 mg of AZD0466. The three dose levels were declared safe by the SRC, which allowed the current study to start dosing patients at 300 mg (dose level 1). A de-escalation to dose level -1 is included as part of the study design with a target dose level of 150 mg. Dose escalation will not be greater than a 2-fold increase of a dose declared tolerable by the SRC.

11.1.3.2 Part A Dose Escalation Scheme

The dose escalation part of the study will enrol up to 48 patients with a histologically confirmed AML, ALL, or intermediate or higher risk MDS to ensure approximately 36 DLT-evaluable patients. At least 3 DLT-evaluable patients are required at each dose level and, up to 12 patients may be enrolled in any dose level. Up to an 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 = 66 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.

11.1.3.3 Dose Escalation, De-escalation, and Stopping Decision Rules

A SRC (Appendix A 5) 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. 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.

A recommended dose level for each subsequent cohort of patients will be made by the SRC, guided by pre-defined decision rules. The decision rules are based on a mTPI-2 design (Guo et al 2017) with a 30% (± 5%) target DLT rate for maximum tolerated dose (MTD). Depending on the number of patients treated at a dose level, and the number of DLTs observed in those patients, the possible decisions will be: to escalate, stay at current dose, de-escalate, or de-escalate and do not use current dose again due to unacceptable toxicity. Decision rules based on mTPI-2 for dose escalation are shown in Table 10.

The decisions on the adequacy of the dose escalation portion of the design were based on outcomes from an internal AZ simulation package which calculates estimates of the likelihood of selecting the true MTD under a range of different scenarios. Operating characteristics are

presented in Table 11.

Table 10 Decision Rules Based on mTPI-2 for Dose Escalation

Number of DLTs	Number of Patients Treated at Current Dose Level											
	n = 1	n = 2	n = 3	n = 4	n = 5	n = 6	n = 7	n = 8	n = 9	n = 10	n = 11	n = 12
0	S[a]	S[a]	E	E	E	E	E	E	E	E	E	E
1	S[b]	S[b]	S	S	E	E	E	E	E	E	E	E
2		DNT	D	D	D	S	S	S	E	E	E	E
3			DNT	DNT	D	D	D	D	S	S	S	E
4				DNT	DNT	DNT	D	D	D	D	D	D
5					DNT	DNT	DNT	DNT	DNT	D	D	D
6						DNT	DNT	DNT	DNT	DNT	DNT	D
7							DNT	DNT	DNT	DNT	DNT	DNT

[a] Adapted from Guo et al 2017 from E to S as a minimum of 3 evaluable patients are needed to make a dose escalation decision.

[b] Adapted from Guo et al 2017 from D to S as a minimum of 3 evaluable patients are needed to make a dose de-escalation decision.

D, de-escalation to the next lower dose level; DLT, dose -limiting toxicity; DNT, dose not tolerated; E, escalation to the next higher dose level; mTPI-2, modified toxicity probability interval; S, stay at the current dose level.

Table 11 Operating Characteristics for Selecting Maximum Tolerated Dose

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CCI

A dose level will be considered as having unacceptable toxicity (with no additional patients to be enrolled at that dose level) if there is an estimated > 95% probability (P) of exceeding the target DLT rate of 30% (ie, P [DLT > 30% data] > 95%) with at least 3 patients treated at that dose level.

If a 'stay' decision is made, additional patients may be enrolled (usually in cohorts of 3) up to a maximum of 12 DLT-evaluable patients for a given dose level.

11.1.3.4 Dose Expansion Design

The dose expansion part of the study will enrol approximately 88 response-evaluable patients, into one of 4 cohorts according to the specific haematological malignancy. Patients will have a histologically confirmed AML or ALL as described below. Cohorts may open either in parallel or sequentially at the sponsor's discretion.

Expansion Cohort B1: Approximately 21 response-evaluable patients with relapsed/refractory AML secondary to myeloproliferative neoplasm (MPN) +/- *TP53* mutation. At least 30% of the cohort should be venetoclax-naïve.

Expansion Cohort B2: Approximately 21 response-evaluable patients with relapsed/refractory AML with *TP53* mutation and no prior history of MPN. At least 30% of the cohort should be venetoclax-naïve.

Expansion Cohort B3: Approximately 25 response-evaluable patients with relapsed/refractory AML without *TP53* mutation or a prior history of MPN (ie, ineligible for Cohort B1 and B2) but have previously been treated with venetoclax.

Expansion Cohort B4: Approximately 21 response-evaluable patients with relapsed/refractory ALL including B-ALL and T-ALL. At least 25% of the cohort should be patients with relapsed and/or refractory T-ALL.

All patients in each cohort will receive study treatment until progressive disease, unacceptable toxicity, or withdrawal of consent.

11.1.4 Benefit-risk Assessment for Module 1

See Section 2.2 of the core protocol for an overall benefit-risk assessment for AZD0466 in the

study population.

The study design for Module 1 includes inter-patient dose escalation and intra-patient dose ramp-up. The dose escalation will commence administration of AZD0466 in patients with AML or ALL at a dose level for which the 2 ramp-up doses are below the dose tolerated as repeated weekly infusions in patients with advanced solid malignancies in Study D8240C00003 (data on file, AstraZeneca). The available nonclinical and clinical information supports an acceptable benefit-risk assessment for investigation of AZD0466 monotherapy in patients with advanced haematological malignancies for which there are limited treatment options.

11.2 OBJECTIVES AND ENDPOINTS - MODULE 1

11.2.1 Primary Objectives

The primary objectives and endpoints for this module are listed in Section 3 of the core protocol; additional endpoints for Part A are listed in Table 12.

Table 12 Primary Objectives - Module 1 - Part A

Objectives	Endpoints/Variables
• To assess the safety and tolerability of AZD0466 in patients with advanced haematological malignancies	• DLT • MTD • RP2D and schedule

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

11.2.2 Secondary Objectives

The secondary objectives and endpoints for this module are listed in Table 13. See Section 3 of the core protocol for all other secondary objectives.

Table 13 Secondary Objectives - Module 1

Objectives	Estimand description
Complete Response Rate (CR+CR$_i$)	

Table 13 Secondary Objectives - Module 1

Objectives	Estimand description
• To estimate the preliminary antitumor activity of AZD0466 by assessment of Complete response rate (CR+CR_i) in patients with advanced haematological malignancies	• Complete response rate (CR+CR_i) is defined as the proportion of patients who have a complete remission (CR) or incomplete haematological response (CR_i), as determined by criteria described in Appendix J, Appendix K and Appendix O). • The analysis will include all dosed patients as intended. • 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+CR_i, 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. • The measure of interest is the estimate of CR+CR_i.
Time to Response (TTR)	
• To estimate the preliminary antitumor activity of AZD0466 by assessment of time to complete response (TTR) in patients advanced haematological malignancies	• Time to response is defined as the time from date of first dose until the date of first documented CR or CR_i. • The analysis will include all dosed patients as intended, who have a complete remission. • Patients who go off study treatment without a clinical response and receive a subsequent therapy and then respond will not be included. • 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+CR_i) until date of documented progression, relapse or failure per Appendix J and Appendix K or death due to any cause. • The analysis will include all dosed patients as intended who have a confirmed response (CR or CR_i), regardless of whether the patient withdraws from study treatment or receives another anticancer therapy. • The measure of interest are the percentiles of DoR.

Table 13 Secondary Objectives - Module 1

Objectives	Estimand description
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. The comparison will include all dosed patients as intended, regardless of whether the patient withdraws from therapy or receives another anticancer therapy. • 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; CR_i, incomplete haematological response; DoR, duration of response; OS, overall survival; TTR, time to response

11.2.3 Exploratory Objectives

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CCI	CCI
CCI	
CCI	
• CCI	• CCI
• CCI	• CCI
• CCI	• CCI
CCI	
• CCI	• CCI
CCI	
• CCI	• CCI

CCI
CCI

11.3 STUDY POPULATION - MODULE 1

Core inclusion and exclusion criteria applicable to all patients enrolled in the study are listed in Section 5.1 and Section 5.2; additional inclusion criteria specific to the dose expansion part

of Module 1 (Module 1 Part B) are listed below in Section 11.3.1. Please note that per core inclusion criterion 4, patients must have received at least one prior line of therapy, and an established standard of care with proven benefit, and for which the patient is eligible, must not be available at the time of enrolment. There are no additional inclusion criteria specific to the dose escalation part of Module 1 (Module 1 Part A). There are no additional exclusion criteria specific to Module 1.

Patients are eligible to be included in the dose escalation part of Module 1 (Module 1 Part A) if they meet all of the inclusion criteria in Section 5.1 and none of the exclusion criteria in Sections 5.2. Under no circumstances can there be exceptions to this rule.

Patients are eligible to be included in the dose expansion part of Module 1 (Module 1 Part B) if they meet all of the inclusion criteria in Section 5.1 and one of the inclusion criteria in Section 11.3.1, and none of the exclusion criteria in Section 5.2. Under no circumstances can there be exceptions to this rule.

Note: Each patient may only be enrolled in one module of this study. A patient who enrols in one module of this study is not eligible to participate in another module.

11.3.1 Inclusion Criteria

Refer to Section 5.1 of the core protocol for the common inclusion criteria applicable to Module 1 Part A dose escalation and Module 1 Part B dose expansion. Additional inclusion criteria for each cohort of Module 1 Part B dose expansion are listed below. Eligible patients with relapsed or refractory AML or ALL will be enrolled to the cohorts according to the inclusion criteria described below.

Expansion Cohort B1

1. Patients must have a diagnosis of AML with a prior history of MPN which is histologically proven based on criteria established by the WHO as documented by medical records.

2. Patients must have received ≤ 2 prior lines of treatment for AML; prior treatment with venetoclax is permitted. A line of treatment is defined as a recognised regimen, as per local or national guidelines, of which the patient has received at least one dose, following which they have relapsed or had refractory disease as defined in Appendix J.

Expansion Cohort B2

1. Patients must have a histologically proven diagnosis of AML, which is based on criteria established by WHO as documented by medical records with a *TP53* mutation. *TP53* status already determined in accordance with local/institutional practice can be used for enrolment but needs to be confirmed centrally. Patients with AML who have had a prior history of MPN are ineligible.

2. Patients must have received ≤ 3 prior lines of treatment for AML; prior treatment with venetoclax is permitted. A line of treatment is defined as a recognised regimen, as per local or national guidelines, of which the patient has received at least one dose, following which they have relapsed or had refractory disease as defined in Appendix J.

Expansion Cohort B3

1. Patients must have a diagnosis of AML, which is histologically proven based on criteria established by WHO as documented by medical records. Patients with AML with the *TP53* mutation (as described for Cohort B2) or AML who have had a prior history of MPN (as described in Cohort B1) are ineligible.

2. Patients must have been previously treated with venetoclax (either as monotherapy or in combination) and have received ≤ 3 prior lines of treatment. A line of treatment is defined as a recognised regimen, as per local or national guidelines, of which the patient has received at least one dose, following which they have relapsed or had refractory disease as in Appendix J.

Expansion Cohort B4

1. Patients must have a diagnosis of ALL, which is histologically proven based on criteria established by WHO as documented by medical records. Patients with T-ALL or B-ALL are eligible for inclusion.

2. Patients must have received ≤ 3 prior lines of treatment. A line of treatment is defined as a recognised regimen, as per local or national guidelines, of which the patient has received at least one dose, following which they have relapsed or had refractory disease as defined in Appendix K.

11.3.2 Exclusion Criteria

Refer to the core protocol (Section 5.2).

11.3.3 Lifestyle Considerations

Patients must comply with the restrictions described in the core study protocol (Section 5.3).

11.3.4 Concomitant Medications

Patients must comply with the restrictions described in the core study protocol (Section 6.5)

11.3.5 Screen Failures

Refer to the core protocol (Section 5.4).

11.4 STUDY TREATMENT - MODULE 1

Information on the preparation, handling, storage, accountability of study treatment measures

to minimise bias, and study treatment compliance and accountability is either provided in Table 15 and/or referenced in the core protocol (Section 6).

11.4.1 Study Treatment – AZD0466

The study treatment investigationalAZD0466 is described in Table 15.

Table 15 Study Treatment for Module 1

Study Treatment	AZD0466
Dosage Form	'AZD0466 powder for concentrate for solution for infusion' supplied with 'Solvent for AZD0466 powder for concentrate for solution for infusion'.
Unit Dose Strength(s)	'AZD0466 powder for concentrate for solution for infusion': 500 mg per vial[a] 'Solvent for AZD0466 powder for concentrate for solution for infusion': 20 mL per vial[a]
Dose Level	As per dose escalation schema (Section 11.1.3.1)
Route of Administration	Intravenous
Handling Instructions	Refer to Handling Instructions
Provider	AstraZeneca R&D
Packaging and Labelling	AZD0466 powder for concentrate for solution for infusion will be provided in 500 mg vials. Each vial will be labelled as per country requirement. Solvent for AZD0466 powder for concentrate for solution for infusion will be provided in 20 mL vials. Each vial will be labelled as per country requirement.

[a] AZD0466 powder for concentrate for solution for infusion 500 mg/vial is intended to be reconstituted with 20 mL custom solvent to produce AZD0466 concentrate for solution for infusion, 25 mg/mL. If required, AZD0466 concentrate for solution for infusion may be further diluted with custom solvent to produce AZD0466 solution for infusion for clinical dosing. Multiple vials of drug product and custom solvent may be used to achieve the required doses.

The dosing and dose escalation scheme are described in Section 11.1.3.1 and the SoA of this module (Section 11.5.1).

Treatment with AZD0466 will commence with a one-week ramp-up followed by weekly administration at the target dose. During ramp-up and while patients are considered at risk of TLS, patients must commence oral allopurinol and encouraged to drink 1.5 to 2 L of fluids at least 24 hours prior to AZD0466 infusion (Appendix F). Intravenous hydration is given on admission as outlined in Appendix F.

This intra-patient dose ramp-up comprises a starting dose on Day 1, subsequent titration to the intermediate dose on Day 4, and to the target dose on Day 8, with weekly IV administration thereafter at the target dose.

The duration of Cycle 1 is 35 days and consists of the 7-day dose ramp-up followed by 28 days of observation during weekly administration at the target dose level (35-day DLT evaluation period, Section 11.4.7). Subsequent cycles are 28 days in duration in which AZD0466 is administered once weekly. All patients will be treated until progressive disease, unacceptable toxicity or withdrawal of consent.

11.4.2 Preparation, Handling, Storage, and Accountability of Study Treatment

Refer to the core protocol (Section 6.2).

11.4.3 Measures to Minimise Bias

Refer to the core protocol (Section 6.3).

11.4.4 Study Treatment Compliance

Refer to the core protocol (Section 6.4).

11.4.5 Concomitant Therapy

Refer to the core protocol (Section 6.5).

11.4.6 Dose Modification

Refer to the core protocol (Section 6.6).

11.4.7 Dose-limiting Toxicity

11.4.7.1 Definition of DLT-evaluable Patients

A DLT-evaluable patient is defined as a patient that has received AZD0466 in Part A and either:

- Has completed the 35-day DLT evaluation period in Cycle 1 and has received at least 75% (3 doses at target dose from Day 8 to Day 29) of the total amount of the planned dose of AZD0466

Or

- Has experienced a DLT during the 35-day DLT evaluation period in Cycle 1.

Patients who have not had a DLT but do not complete the 35-day DLT evaluation period may be replaced to achieve the required minimum number of DLT-evaluable patients for each cohort (Section 11.1.3.4). All DLT-evaluable patients enrolled during the dose-escalation stage will be evaluated in order to determine the MTD and RP2D.

11.4.7.2 Dose-limiting Toxicity

Any event that meets the DLT criteria in the opinion of the Investigator should be reported to the Medical Monitor within 24 hours of knowledge of the event. Events will be assessed for DLT criteria according to the CTCAE National Cancer Institute (NCI) v5.0 (Section 8.3.2) except for TLS, which will be assessed for DLT criteria using the Howard modification of Cairo-Bishop criteria (Appendix G). Toxicity that is clearly and directly related to the underlying malignancy or to an extraneous cause is excluded from the definition of a DLT. A DLT will be defined as the occurrence of any of the following:

- Any CTCAE Grade 3 non-haematological toxicity lasting > 7 days OR any CTCAE Grade 4 non-haematological toxicity, with the exception of:
  - CTCAE Grade 4 nausea, vomiting, or diarrhoea lasting < 7 days in the absence of maximum supportive therapy,
  - Elevation in serum amylase and/or lipase without clinical or radiographic evidence of pancreatitis,
  - CTCAE Grade 3 fatigue, asthenia, fever, anorexia, or constipation.
- Any other cardiac findings of CTCAE Grade ≥ 2 if considered by the Investigator to be clinically significant.
- AZD0466 should be permanently discontinued if a CTCAE Grade ≥ 3 cardiac AE of any duration occurs at any time during study treatment, if considered by the Investigator to be related to study treatment.
- AZD0466 should be permanently discontinued if liver function test abnormalities meets Hy's Law (HL) or Potential Hy's Law (PHL) criteria, and considered by the Investigator to be related to study treatment (see Appendix E).
- Prolonged myelosuppression: as myelosuppression and cytopenias are expected outcomes of leukaemia treatment, only the criteria defined below will be a DLT:
  - Lack of haematological recovery (ANC remaining <0.5x 10^9/L, platelets remaining < 50 x 10^9/L) in the absence of active leukaemia in bone marrow (blasts < 5%) and with marrow hypocellularity at < 5% by Day 42.
- Cairo-Bishop Grade ≥ 3 Clinical TLS (Appendix G) that occurs despite protocol-recommended management.
- Cairo-Bishop Laboratory TLS (Appendix G) with metabolic abnormalities that do not resolve within 5 days despite protocol-recommended management.
- Any other toxicity that
  - is greater than at baseline, is clinically significant and/or unacceptable, and is judged to be a DLT by the SRC, or
  - results in a disruption of dosing schedule of more than 21 days.

Dose-limiting toxicities will not include the following:

- Transient isolated laboratory abnormalities, which are not considered clinically significant and resolve to baseline within 72 hours without any intervention.
- Any documented infection (including COVID-19), bleeding or other direct complication of cytopenia due to active underlying disease.

The DLT evaluation period remains at 35 days for patients with active bone marrow disease by Day 35, irrespective of the blood counts. The DLT evaluation period may be extended to include a repeat bone marrow assessment on Day 42, in the event of myelosuppression (see Table 6).

11.4.7.3 Definition of Maximum Tolerated 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.
- In the case of dose levels with estimated toxicity of equal distance from the target toxicity of 30% (tied dose levels), the following approach will be used (Ji et al 2010); among all tied dose levels the highest dose level with target toxicity ≤ 30% will be selected, unless all tied dose levels have estimated toxicity > 30%, in which case the lowest dose level will be selected.
- If the estimated DLT rate is > 30% for all doses, then select the lower dose among the tied doses.

11.4.7.4 Definition of Recommended Phase II Dose

The RP2D and schedule will be determined in discussion among the SRC (Appendix A 5) and the sponsor. Observations related to PK, PD, and AEs may be included in the rationale supporting the RP2D and schedule.

11.4.7.5 Definition of Maximum Feasible Dose

A dose and schedule will be considered non-feasible and escalation will cease where the maximum dose permitted based on the Chemistry Manufacturing and Controls (CMC) quality specifications (currently set against a maximum weekly dose of 6000 mg) has been reached.

11.4.7.6 Safety Review Committee

Once there are at least 3 evaluable patients at the dose level during the dose escalation phase of the study, the SRC (Appendix A 5) will evaluate all available safety, tolerability, and PK of AZD0466, as well as the recommendation from the mTPI-2 model, to decide the next dose.

This decision may be to escalate, to stay at the current dose, de-escalate, or to de-escalate and declare that the current dose is unsafe. If a stay decision is made, additional subjects may be enrolled up to a maximum of 12 subjects for a given dose cohort. The mTPI-2 has been employed to improve the rate of accrual of patients to cohorts nearer the presumed therapeutic dose by reducing the need for late replacement of patients who become non-evaluable during the 35-day assessment period while not compromising collection of safety data (Davids et al 2017). When there are other patients that are ongoing at the time of this review, the SRC may decide to defer their decision until these further patients become evaluable.

Any patient started on treatment in error, who has failed to comply with all of the selection criteria but meets the criteria of an evaluable patient, will be reviewed on a case-by-case basis by the SRC to determine if the patient should be included or excluded in the decision for dose escalation.

The decisions and decision-making of the SRC on the next dose level will be documented and provided to the Investigators prior to dosing any new patients.

11.4.7.7 Expansion Cohorts (Part B) - Module 1

Sponsor approval will be required to open the individual expansion cohorts.

11.4.7.8 Discontinuation of AZD0466 and Patient Withdrawal from Study

Refer to the core protocol (Section 7).

11.4.8 Intervention After the End of the Study

Refer to the core protocol (Section 6.8).

11.5 STUDY PLAN AND TIMING OF PROCEDURES – MODULE 1

11.5.1 Schedule of Activities

The SoA for Cycle 1, Cycles 2 onwards, and follow-up periods are shown respectively in Table 16 and Table 17 for both Part A and Part B. Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. Whenever ECGs, vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in the SoAs.

Table 16 Module 1 - Schedule of Activities for Screening and Cycle 1 (Parts A and B)

Procedure	Screening	Cycle 1 (35 days)																	Details in CSP Section
		Ramp-up 1			Ramp-up 2[a]				Target dose										
Day	-28 to -1	1	2	3	4	5	6	7	8	9	10	11	15	16	22	23	29	30	
Visit window		± 2 days[b]																± 1 day	
Informed consent	X																		Appendix A 3
Inclusion and exclusion criteria	X																		5.1; 5.2; 11.3.1; 11.3.2
Demography	X																		8
Medical history	X																		8
Physical examination	X	X	X		X	X			X	X			X	X	X	X	X	X	11.6.2.1
Height	X																		11.6.2.3
Weight	X	X							X						X				11.6.2.3
Chest X-ray[c]	X																		11.6.2.4
Vital signs[d]	X	X*			X*				X*	X	X	X	X*		X*		X*	X[e]	11.6.2.5
ECOG performance status	X	X																	11.6.2.8
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
CCI [redacted]	X																		8.6.1.1
Safety ECGs (triplicate)[f]	X	X*	X		X*	X			X*	X	X	X	X*	X	X*	X	X*	X	11.6.2.6
24 h continuous 12-lead ECG recording for PK (Holter)									X	X									11.6.2.6
Cardiac MUGA/MRI/ ECHO[g]	X																		11.6.2.7

Table 16 Module 1 - Schedule of Activities for Screening and Cycle 1 (Parts A and B)

Procedure	Screening	Cycle 1 (35 days)																	Details in CSP Section
		Ramp-up 1			Ramp-up 2[a]				Target dose										
Day	-28 to -1	1	2	3	4	5	6	7	8	9	10	11	15	16	22	23	29	30	
Visit window		± 2 days[b]																± 1 day	
Laboratory Tests																			
COVID-19 test	X																		11.6.2.9.1
Hepatitis B and C, HIV and CMV	X																		11.6.2.9.2
Pregnancy test (WOCBP)	X	X																	11.6.2.9.3
CBC with differential [redacted][h]	X	X*	X		X*	X			X*	X			X	X	X	X	X	X[e]	11.6.2.9.6
Clinical chemistry	X	X	X		X	X			X	X			X	X	X	X	X	X	11.6.2.9.4
TLS Monitoring[i]		X*	X*		X*	X*			X*	X*			X*	X*	X*	X*	X*	X*	11.6.2.9.12 and 11.6.2.9.13
CPK	X	X	X		X	X			X	X			X	X	X	X	X	X	11.6.2.9.4
Coagulation indices	X	X			X				X				X		X		X		11.6.2.9.7
Cardiac troponin I[j]	X																		11.6.2.9.8
BNP (or NTproBNP)	X																		11.6.2.9.8
Cortisol, ACTH, TSH	X								X										11.6.2.9.9
Amylase and lipase	X	X			X				X				X		X		X		11.6.2.9.5
Serum immunoglobulins[k]	X								X										11.6.2.9.10
Urinalysis	X	X			X				X				X		X		X		11.6.2.9.11
[redacted]		[redacted]																	[redacted]
[redacted]		[redacted]																	[redacted]

Table 16 Module 1 - Schedule of Activities for Screening and Cycle 1 (Parts A and B)

Procedure	Screening	Cycle 1 (35 days)																	Details in CSP Section
		Ramp-up 1			Ramp-up 2[a]				Target dose										
Day	-28 to -1	1	2	3	4	5	6	7	8	9	10	11	15	16	22	23	29	30	
Visit window		± 2 days[b]																± 1 day	
Overnight inpatient stay		X**			X**				X**				X**		X**		X**		11.6.2.9.12
Administer AZD0466		X			X				X				X		X		X		6.1
Pharmacokinetic Assessments[l]																			
Blood sample for plasma PK		X*			X*				X*	X	X	X						X[m] Part B	11.6.3.1.2
Urine PK collection (Part A select cohort(s) only)		X*	X		X*	X			X*	X									11.6.3.1.1
Pharmacodynamic Assessments																			
CCI																			
CCI																			
Blood for peripheral blood smears (Part A only cohorts)	X	X*	X		X*	X			X*	X									11.6.3.2.3
CCI																			
CCI																			
CCI																			

Table 16 Module 1 - Schedule of Activities for Screening and Cycle 1 (Parts A and B)

Procedure	Screening	Cycle 1 (35 days)																	Details in CSP Section
		Ramp-up 1			Ramp-up 2[a]				Target dose										
Day	-28 to -1	1	2	3	4	5	6	7	8	9	10	11	15	16	22	23	29	30	
Visit window		± 2 days[b]																± 1 day	
CCI [redacted]	[redacted]	[redacted]	[redacted]																[redacted]
CCI [redacted]	[redacted]	[redacted]																[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]																	[redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]						[redacted]						[redacted]			[redacted]	[redacted]
Disease Assessment																			
Mandatory bone marrow biopsy and aspirate for disease assessment CCI [redacted]	X																	X	11.6.1; CCI [redacted]
MRD (Part B expansion only)	X																	X	11.6.1.4
CT/MRI/PET scans (only if extramedullary disease)	X																	X	8.1.1

[a] Any visits (eg, Day 6 and Day 7) that do not require attendance at the site for blood draw or physical examination can be conducted by telephone, at the Investigator's discretion.

[b] The Days 1, 4 and 8 ramp-up dose administration should be at least 72 h apart.

[c] Chest X-rays may also be performed at other timepoints during the study at the Investigator's discretion, when clinically indicated.

[d] On PK sampling days, blood pressure readings to be taken at each PK sample timepoint. All blood pressure readings can be taken ±10 minutes from the designated PK sample collection.

[e] At disease assessment if disease assessment is not on Day 30.

[f] On PK sampling visits, triplicate ECGs will be collected before the PK sample is taken (please refer to Section 11.6.3.1.2 for additional PK assessments).

[g] Cardiac MUGA/MRI/ECHO to assess left ventricular ejection fraction will be conducted. Ensure the same modality is used for each patient.

[h] CCI [redacted].

[i] At least twice in the first 24 hours after each administration of AZD0466 and as clinically indicated thereafter as per institutional protocol.
[j] Cardiac troponin to be collected at screening (baseline) and at other timepoints in the study, as clinically indicated. Cardiac troponin I is preferred when available, however if not, cardiac troponin T is acceptable. To allow comparison with baseline, sites are requested to maintain consistency with the troponin assay used.
[k] Routine serum immunoglobulin profile (IgA, IgG, IgM).
[l] Samples for PK assessments must be collected relative to the time of dosing as specified in Section 11.6.3.1.
[m] Sample to be collected at every MRD assessment.
[n] CCI [redacted]
[o] At screening to be collected between Day -28 and -1. If performed on day of infusion must be at least 6 hours post-infusion. When it is not possible to obtain a new bone marrow biopsy, a historic bone marrow biopsy sample may be used if collected within 28 days of first dose of AZD0466, but a historic bone marrow biopsy sample collected within 14 days of the first dose is preferred.

*Indicates more than one assessment is to be performed at the visit.
**Overnight stays are recommended on infusion days during Cycle 1, but patients may be discharged prior to 24 hours post-dose, as per investigator discretion, if their TLS laboratory values are appropriate, and if the patient is able to return for a follow-up clinic visit to complete required safety and laboratory assessments within the specified time windows (Section 11.6.2.9.12).
ACTH, adrenocorticotropic hormone; BNP, brain natriuretic peptide; CBC, complete blood count; CCI [redacted] CCI [redacted]; CMV, cytomegalovirus; COVID-19, Coronavirus disease 2019; CPK, creatine phosphokinase; D, Day; CCI [redacted]; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; MRD, minimal/measurable residual disease; MRI, magnetic resonance imaging; MUGA, multigated acquisition; CCI [redacted]; PET, positron emission tomography; PK, pharmacokinetic; CCI [redacted]; RU, ramp-up; TSH, thyroid stimulating hormone; TLS, tumour lysis syndrome; WOCBP, women of childbearing potential.

Table 17 Module 1 - Schedule of Activities for Treatment Cycle 2 and Beyond and Follow-up Periods (Part A and B)

Procedure	Cycle 2 (28 days)				Cycle 3 and beyond (28 days)					Follow-up			Details in CSP Section
										EoT	Post treatment follow-up[a]	Survival follow-up	
Day	**1**	**2**	**8/15/22**	**9/16/23**	**1**	**2**	**8**	**9/16/23**	**15/22**		**28 days after last dose**	**Every 1 month after last dose**	
Visit window	**±2 days**									**±7 days**	**±7 days**	**±14 days**	
Physical examination	X	X	X	X	X	X	X	X	X	X			11.6.2.1
Weight	X		D15		X				D15	X			11.6.2.3
Vital signs[b]	X*	X	X*	D23-28 with disease assessment	X*		X*	D23-28 with disease assessment	X*	X			11.6.2.5
ECOG performance status	X				X					X			11.6.2.8
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X		6.5
Adverse events	X	X	X	X	X	X	X	X	X	X	X		8.3
Safety ECGs (triplicate)	X*				X* (even cycles only from C4)					X			11.6.2.6
Cardiac MUGA/MRI/ECHO[c]			D8				Every 3 cycles from C5			X			11.6.2.7
Laboratory Tests													
COVID-19 test	X				X					X			11.6.2.9.1
Pregnancy test (WOCBP)	X				X					X			11.6.2.9.3
CBC with differential CCI [redacted][d]	X	X	X	X[e]	X	X	X	X[e]	X	X			11.6.2.9.6

Table 17 Module 1 - Schedule of Activities for Treatment Cycle 2 and Beyond and Follow-up Periods (Part A and B)

Procedure	Cycle 2 (28 days)				Cycle 3 and beyond (28 days)					Follow-up			Details in CSP Section
										EoT	Post treatment follow-up[a]	Survival follow-up	
Day	1	2	8/15/22	9/16/23	1	2	8	9/16/23	15/22		28 days after last dose	Every 1 month after last dose	
Visit window	±2 days									±7 days	±7 days	±14 days	
Clinical chemistry	X	X	X	X	X	X	X	X	X	X			11.6.2.9.4
CPK	X	X	X	X	X	X	X	X	X	X			11.6.2.9.4
Coagulation indices	X		X		X		X		X	X			11.6.2.9.7
Cortisol, ACTH, TSH										X			11.6.2.9.9
Amylase and Lipase	X		X		X		X		X	X			11.6.2.9.5
Serum immunoglobulins										X			11.6.2.9.10
Urinalysis	X		X		X		X		X	X			11.6.2.9.11
Administer AZD0466	X		X		X		X		X				6.1
Pharmacokinetic Assessments													
Blood sample for plasma PK	X*	X		D23-28 (Part B)[f]	X*			D23-28 (Part B)[f]					11.6.3.1.2
Pharmacodynamic Assessments													
[redacted]	[redacted]	[redacted]			CCI [redacted]	[redacted]				[redacted]			[redacted]
CCI [redacted]	[redacted]	[redacted]								[redacted]			[redacted]
Blood for peripheral blood smears (Part A cohorts only)	X	X								X			11.6.3.2.3

Table 17 Module 1 - Schedule of Activities for Treatment Cycle 2 and Beyond and Follow-up Periods (Part A and B)

Procedure	Cycle 2 (28 days)				Cycle 3 and beyond (28 days)					Follow-up			Details in CSP Section
										EoT	Post treatment follow-up[a]	Survival follow-up	
Day	1	2	8/15/22	9/16/23	1	2	8	9/16/23	15/22		28 days after last dose	Every 1 month after last dose	
Visit window	±2 days									±7 days	±7 days	±14 days	
CCI													
CCI													
CCI													
CCI													
CCI													
CCI													
					CCI								
Disease Assessment													
Mandatory bone marrow biopsy and aspirate for disease assessment CCI [g]				D23-28				D23-28		X[h]			11.6.1; CCI

Table 17 Module 1 - Schedule of Activities for Treatment Cycle 2 and Beyond and Follow-up Periods (Part A and B)

Procedure	Cycle 2 (28 days)				Cycle 3 and beyond (28 days)					Follow-up			Details in CSP Section
										EoT	Post treatment follow-up[a]	Survival follow-up	
Day	1	2	8/15/22	9/16/23	1	2	8	9/16/23	15/22		28 days after last dose	Every 1 month after last dose	
Visit window	±2 days									±7 days	±7 days	±14 days	
MRD (Part B expansion only)				D23-28 at disease assessment				C4 D23-28 at disease assessment and every 3 cycles until disease progression (D23-28 at disease assessment)[h]		X[h]			11.6.1.4
CT/MRI/PET scans (only if extramedullary disease)								Every 3 cycles from C3, D23-28		X			8.1.1
Survival follow up												X	8

[a] Patients will be followed during the off-treatment period until all treatment related toxicity resolves, or for at least 28 days post-study drug discontinuation or until new therapy. This can be done via telephone contact at the Investigator's discretion.
[b] On PK sampling days, blood pressure readings to be taken at each PK sample timepoint. All blood pressure readings can be taken ± 10 minutes from the designated PK sample collection.
[c] Cardiac MUGA/MRI/ECHO to assess left ventricular ejection fraction will be conducted. Ensure the same modality is used for each patient. Unscheduled assessment if deemed clinically warranted.
[d] CCI [redacted]
[e] If disease assessment is not on Day 23, an additional CBC sample is required.
[f] CCI [redacted]
[g] If performed on day of infusion must be at least 6 hours post-infusion.
[h] Bone marrow evaluation at EoT only required if not performed in the preceding 21 days.
*Indicates more than one assessment is to be performed at the visit.

ACTH, adrenocorticotropic hormone; C, cycle; CBC, complete blood count; CCI ; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; CPK, creatine phosphokinase; D, Day; CCI ; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EoT, end of treatment; HIV, human immunodeficiency virus; MRD, minimal/measurable residual disease; MRI, magnetic resonance imaging; MUGA, multigated acquisition; CCI ; PET, positron emission tomography; PK, pharmacokinetic; CCI ; RU, ramp-up; TSH, thyroid stimulating hormone; TLS, tumour lysis syndrome; WOCBP, women of childbearing potential.

11.6 STUDY ASSESSMENTS AND PROCEDURES - MODULE 1

Study procedures and their timings for this module are summarised in the SoA (Section 11.5.1). Patient demographic characteristics, medical history, and disease characteristics will be recorded as described in Section 8, Enrolment and Screening.

11.6.1 Efficacy Assessments

11.6.1.1 Peripheral Blood

Peripheral blood will be collected for complete blood count (CBC) (laboratory safety assessment) as indicated in the SoA (Table 16 and Table 17). CCI [redacted]

11.6.1.2 Extramedullary Disease

Refer to the core protocol (Section 8.1.1) for details on disease assessment for extramedullary disease.

11.6.1.3 Bone Marrow

Bone marrow core biopsy and bone marrow aspirate should be performed (as specified in Table 16 and Table 17) as below. In Module 1 Part A, in the event that a patient is otherwise eligible but extenuating circumstances preclude obtaining a new on-study bone marrow biopsy, a historic bone marrow biopsy sample may be used if collected within 28 days of first dose, but within 14 days is preferred, with the approval of the Medical Monitor.

Mandatory biomarker analysis (Section 11.6.4.1.6) will be performed any time a bone marrow analysis is performed. If performed on a dosing day, this must be at least 6 hours post-infusion.

- Screening (between Day -28 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.

11.6.1.4 Minimal/Measurable Residual Disease (Part B Only)

Bone marrow sample collections for minimal/measurable residual disease (MRD) assessments will be performed (as specified in Table 16 and Table 17) at the following times for Part B only:

- Screening
- Cycle 1 Day 30 ± 1 day at the time of disease assessment
- Cycle 2 between Days 23 to 28 at the time of disease assessment
- Cycle 4 between Days 23 to 28 at the time of disease assessment
- At any morphologic remission timepoint. If unable to collect the bone marrow sample on the day of CR/CR_i, additional sample need to be collected either within 4 weeks, or at the next visit.
- CCI [redacted]
- CCI [redacted]
- Patients will be monitored every 3 cycles (or at the discretion of the Investigator, in line with scheduled response assessments) thereafter until disease progression (or up to 2 years after $CR_{MRD-NEG}$ confirmation, at the discretion of the Investigator).
- End of Treatment/Disease progression.

11.6.1.5 Survival Follow-up

Refer to the core protocol (Section 8, Follow-up Period)

11.6.2 Safety Assessments

11.6.2.1 Physical Examination

A complete physical examination will be performed and include assessments of the following: general appearance, abdomen, skin, head, and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, respiratory, cardiovascular, musculoskeletal (including spine and extremities), and neurological systems. Investigators should pay special attention to clinical signs related to previous serious illnesses. New or worsening abnormalities may qualify as AEs (see Section 8.3.5 for details). Targeted physical examinations will be performed throughout the treatment period, at the discretion of the Investigator eg, for new or worsening symptoms and/or signs.

Physical examinations in the Part A and Part B should be performed (as specified in the SoA in Table 16 and Table 17) as follows:

- Screening
- Cycle 1: pre-infusion on each dosing day and on the calendar day after the dosing day
- Cycle 2 and beyond: pre-infusion on each dosing day and on the calendar day after the dosing day
- EoT visit.

11.6.2.2 Medical History

Refer to the core protocol Section 8, Enrolment and Screening.

11.6.2.3 Height and Body Weight

Height will be recorded at screening.

Body weight will be assessed (as specified in the SoA in Table 16 and Table 17) as follows:

- Screening
- Cycle 1 Day 1, 8, and 22: pre-infusion
- Cycle 2 and beyond Day 1 and Day 15: pre-infusion
- EoT visit

11.6.2.4 Chest X-ray

Chest x-ray will be performed at screening to provide a baseline against which potential treatment-emergent lung abnormalities may be evaluated. Chest x-rays may also be performed at other timepoints during the study at the Investigator's discretion, when clinically indicated.

11.6.2.5 Vital Signs

Vital signs will include heart rate, pulse, systolic and diastolic blood pressure (BP), respiration rate, height (at screening), and temporal temperature. Blood pressure and pulse measurements will be assessed in a seated or semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available. Measurements should be preceded by at least 10 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).

On PK sampling days, BP readings to be taken at each PK sample timepoint. All BP readings can be taken ±10 minutes from the designated PK sample collection.

Vital signs should be assessed (as specified in the SoA in Table 16 and Table 17) as follows:

- Screening
- Cycle 1 Day 1: pre-infusion, 30 minutes (±5 minutes) after the start of the infusion, at the end of the infusion (+10 minutes)
- Cycle 1 Day 4: pre-infusion, 30 minutes (±5 minutes) after the start of the infusion, at the end of the infusion (+10 minutes)
- Cycle 1 Day 8: pre-infusion, 30 minutes (±5 minutes) after the start of the infusion, at the end of the infusion (+10 minutes), 2 hours (±15 minutes), 6 hours (±30 minutes), and 9 hours (±1 hour) after the start of the infusion

- Cycle 1 Day 9: 24 hours (±2 hours) after the start of the Day 8 infusion
- Cycle 1 Day 10: 48 hours (±3 hours) after the start of the Day 8 infusion
- Cycle 1 Day 11: 72 hours (±7 hours) after the start of the Day 8 infusion
- Cycle 1 Day 15, 22, and 29: pre-infusion, 30 minutes (±5 minutes) after the start of the infusion, at the end of the infusion (+10 minutes)
- Cycle 1 Day 30 ± 1 day at the time of disease assessment
- Cycle 2 Day 1: pre-infusion, 30 minutes (±5 minutes) after the start of the infusion, at the end of the infusion (+10 minutes), 2 hours (±15 minutes), 6 hours (±30 minutes), and 9 hours (±1 hour) after the start of the infusion
- Cycle 2 Day 2: 24 (±2 hours) hours after the start of the Day 1 infusion
- Cycle 2 Day 8, 15, and 22: pre-infusion, 30 minutes (±5 minutes) after the start of the infusion, at the end of the infusion (+10 minutes)
- Cycle 2 between Days 23 to 28 at the time of disease assessment
- At each cycle from Cycle 3 and beyond Day 1, 8, 15, and 22: pre-infusion, 30 minutes (±5 minutes) after the start of the infusion, at the end of the infusion (+10 minutes)
- Cycle 3 and beyond Days 23 to 28 at the time of disease assessment
- EoT visit

11.6.2.6 Electrocardiograms

Digital 12-lead ECGs (triplicate ECGs, all 3 within a 5-minute time period) will be obtained after the patient has been resting in a supine position for at least 10 minutes. ECGs will be measured before vital signs and prior to PK blood draws at all matched PK sample timepoints. A standardised ECG machine provided by the central ECG vendor should be used and the patient should be examined using the same machine throughout the study, where feasible.

If an unscheduled ECG is done at any time, then an electrolyte panel (Section 11.6.2.9) must be collected to coincide with ECG testing.

Central ECG reads will be utilised during this study. Standard ECG parameters to be determined will include HR/RR, PR, QRS, QT, and QTcF (QT interval corrected for HR using Fridericia's formula) intervals.

After the ECGs have been recorded, the Investigator or designated physician will review each of the ECGs at all timepoints for the presence of abnormalities (including rhythm, ECG intervals, or repolarisation abnormalities) and may refer to a local cardiologist if appropriate. A paper copy of the ECG should be filed in the patient's medical records. For all ECGs, an overall evaluation and interpretation should be recorded by the Investigator or designated physician. Any clinically significant abnormalities detected require a confirmatory ECG. In

case that the centrally provided ECG machine is unavailable or technical issues occur that preclude correct measurement, local ECGs (using the site owned device) may be performed instead.

See Section 6.6.5 for management of cardiac findings and cardiovascular parameters that require treatment to be withheld or increased monitoring. Twelve-lead centrally-read digital ECGs will be performed in triplicate and should be assessed as specified in the SoA (Table 16 and Table 17), and in Table 18).

Table 18 Safety ECG Timepoints and Holter ECG extractions (Module 1)

			Part A and Part B	
Study period	**Day**	**Timepoint**	**Holter ECG extractions** (for PK purpose)	**Triplicate Safety ECGs** (for safety purpose)
Screening	-28 to -1	Baseline	-	X
Cycle 1	1	Pre-infusion	-	X[a]
		End of the infusion (+10 min)	-	X[a]
	2	24 hours after the start of the Day 1 infusion (± 2 hours)		X
	4	Pre-infusion	-	X[a]
		End of the infusion (+10 min)	-	X[a]
	5	24 hours after the start of the Day 4 infusion (±2 hours)		X
	8	Pre-infusion	X	X[a]
		30 min after start of infusion (±5 min)	X	-
		End of the infusion (+10 min)	X	X[a]
		2 hours from start of Day 8 infusion (±15 min)	X	-
		6 hours from start of Day 8 infusion (±30 min)	X	-
		9 hours from start of Day 8 infusion (±1 hour)	X	-
	9	24 hours after the start of the Day 8 infusion (±2 hours)	X	X[a]
	10	48 hours after the start of the Day 8 infusion (± 3 hours)	-	X[a]
	11	72 hours after the start of the Day 8 infusion (±7 hours)	-	X[a]
	15	Pre-infusion	-	X
		End of the infusion (+10 min)	-	X
	16	24 hours after the start of the Day 15 infusion (±2 hours)	-	X
	22	Pre-infusion	-	X
		End of the infusion (+10 min)	-	X

	23	24 hours after the start of the Day 22 infusion (±2 hours)	-	X
	29	Pre-infusion	-	X
		End of the infusion (+10 min)	-	X
	30	24 hours (±2 hours) after the start of the Day 29	-	X[a]
Cycle 2 and even cycles thereafter	1	Pre-infusion	-	X[a,b]
		End of the infusion (+10 min)	-	X[a,b]
End of Treatment			-	X

[a] At PK sampling visits, triplicate ECGs will be collected before the PK sample is collected (please refer to Section 11.6.3.1.2 for additional PK assessments).
[b] Beyond Cycle 2 ECGs will be collected on Day 1 of even cycles only, ie, Cycle 4, 6, 8 etc.: pre-infusion and at the end of the infusion (+10 minutes).

11.6.2.6.1 Continuous 12-lead ECG Recordings (Holter)

Continuous recordings of 12-lead ECGs (12-lead Holter devices) will be performed for the purpose of PK modelling, which allows monitoring of PR, QRS, QT, QTcF, RR intervals, and arrhythmia and to allow extraction of replicate 12-lead ECGs. The timing of ECGs may be altered depending on the emerging PK profile. Recording should be performed (as specified in the SoA in Table 16 and Table 18) on Day 8 of Cycle 1, with recording commencing pre-infusion to cover the 24-hour timepoint (prior to PK sampling). The standardised 12-lead Holter device will be provided by the central ECG vendor who will provide the central ECG reads.

The 12-lead Holter devices will always be fitted and safely removed by the Investigator or a trained designee.

The schedule of continuous ECG recordings may be increased, reduced, or stopped at any time during the study, if supported by emerging data and with the agreement of the SRC.

11.6.2.7 Cardiac MUGA/MRI/ECHO

A cardiac MUGA/MRI/ECHO to assess LVEF will be conducted. The modality of the cardiac function assessments must be consistent within a patient ie, if ECHO is used for the screening assessment then ECHO should also be conducted at subsequent assessments. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study treatment, to confirm reversibility of the abnormality. The patients should also be examined using the same machine and operator whenever possible.

Unscheduled assessments should be performed as clinically indicated, including after a clinically significant ECG finding (T wave inversion/flattening, significant QRS amplitude changes or symptomatic patient, etc). In case of any T wave abnormality, the ECHO, MRI, or MUGA should be repeated at the EoT visit to address the question of recovery during the off-treatment period.

Cardiac MUGA/MRI/ECHO should be performed (as specified in the SoA in Table 16 and Table 17) as follows:

- Screening
- Cycle 2 Day 8
- Every third cycle from Cycle 5 (ie, Cycle 5, 8, 11, etc) on Day 8
- EoT visit

11.6.2.8 Performance Status

ECOG performance status (Appendix L) will be assessed at the times specified in the SoA (Table 16 and Table 17) as follows:

- Screening
- Every Cycle Day 1
- EoT visit

11.6.2.9 Clinical Safety Laboratory Assessments

Clinical laboratory safety tests, including urine or serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

Laboratory values will be repeated, confirmed, and followed up as appropriate.

Safety laboratory assessments will be performed at the timepoints specified in the SoA (Table 16 and Table 17) Collection times begin from the start of the infusion.

Following SRC review of emerging data, the timing of laboratory safety assessment samples may be adjusted for subsequent cohorts. Additional sampling times may be added or removed if indicated by the emerging data.

11.6.2.9.1 COVID-19 Testing

COVID-19 tests will be conducted where appropriate and in accordance with local procedures. COVID-19 testing may include nucleic acid/PCR and/or serological approaches. This should be performed as follows:

- Screening: patients with a positive PCR test results must be antigen negative with confirmed IgG antibodies to COVID-19 to be able to start treatment

- At each cycle from Cycle 2 onwards Day 1: pre-infusion
- EoT visit

11.6.2.9.2 Viral Serology

A Hepatitis B, Hepatitis C, HIV, and CMV viral serology sample will be collected at screening. If a patient was found to have positive anti-HBc antibody and a negative HBsAg, a DNA PCR test will be done to determine eligibility criteria.

11.6.2.9.3 Pregnancy Test (Women of Childbearing Potential Only)

A urine/serum sample for a pregnancy test will be collected from all women of childbearing potential (defined in Section 5.3) as follows:

- Screening
- Day 1 of each treatment cycle: pre-infusion
- EoT visit

11.6.2.9.4 Clinical Chemistry

Blood samples for determination of clinical chemistry will be collected as specified in Table 16 and Table 17. Unscheduled samples may be collected if deemed clinically warranted, and results of unscheduled assessment should be recorded in the eCRF.

If an unscheduled ECG is performed for patient assessment, an electrolyte panel (ie, calcium, magnesium potassium) must be done. If clinically indicated, a troponin assay should coincide with this evaluation. Cardiac troponin I is preferred when available, however if not, cardiac troponin T is acceptable. To allow comparison with baseline, sites are requested to maintain consistency with the troponin assay used. Isolated troponin elevations are not sufficient to trigger dosing changes and should be evaluated in the context of other cardiac findings.

The following clinical chemistry tests will be performed (Table 19):

Table 19 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[b]	Total protein
Bilirubin (total and direct)	Lactate dehydrogenase	Chloride
Blood urea nitrogen	Lipase[c]	Uric acid
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] Glutamate dehydrogenase testing is optional, but should be performed where sites have the capability to perform the test locally.
[c] Collected at screening, pre-infusion on each dosing day, and end of treatment visit.
NB. Refer to Appendix E if alanine amino transferase or aspartate aminotransferase ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN.
ULN, upper limit of normal range.

Results for LFTs must be available and reviewed before infusion of study treatment throughout Cycle 1 and review of results is recommended before each administration of study treatment from Cycle 2 and beyond. Values must have returned to the patient's baseline before infusion of AZD0466.

Clinical chemistry, including creatine phosphokinase, should be performed for Part A and B according to the schedule below.

- Screening
- Pre-infusion on each dosing day
- 24 hours (±2 hours) after each dosing
- EoT visit

11.6.2.9.5 Amylase and Lipase

Amylase and lipase will be collected for Part A and Part B according to the schedule below.

- Screening
- Pre-infusion on each dosing day
- EoT visit

11.6.2.9.6 Complete Blood Count with Differential [redacted]

Complete blood counts with differential [redacted] (Table 20) will be collected for Part A and Part B. Part of the blood sample collected for CBC will be used for peripheral blood smears as detailed in Section 11.6.1.

Table 20 Haematology Assessments

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

Collection times for Part A and Part B are indicated below (collection time begins from start of infusion).

- Screening
- Cycle 1 Day 1: pre-infusion, end of infusion (+10 minutes), 6 hours (±30 minutes) after the start of the infusion
- Cycle 1 Day 2: 24 hours (±2 hours) after the Day 1 infusion
- Cycle 1 Day 4: pre-infusion, end of infusion (+10 minutes)
- Cycle 1 Day 5: 24 hours (±2 hours) after the Day 4 infusion
- Cycle 1 Day 8: pre-infusion, at the end of infusion (+10 minutes), 2 hours (±30 minutes) 6 hours (±30 minutes), 9 hours (±1 hour) after the start of the infusion
- Cycle 1 Day 9: 24 hours (±2 hours) after the Day 8 infusion
- Cycle 1 Day 15: pre-infusion
- Cycle 1 Day 16: 24 hours (±2 hours) after the Day 15 infusion
- Cycle 1 Day 22: pre-infusion
- Cycle 1 Day 23: 24 hours (±2 hours) after the Day 22 infusion
- Cycle 1 Day 29: pre-infusion
- Cycle 1 Day 30: 24 hours (±2 hours) after the Day 29 infusion (and at disease assessment if disease assessment is not on Day 30)
- At each cycle from Cycle 2 onwards: pre-infusion on each dosing day
- At each cycle from Cycle 2 onwards: 24 hours (±2 hours) after each dosing
- At each disease assessment
- EoT visit

11.6.2.9.7 Coagulation Indices

Prothrombin time (PT), international normalisation ratio (INR), and partial thromboplastin time (PTT) will be collected as specified in the individual modules. INR assessment should be repeated if any abnormalities above ULN in liver biochemistry occur, at 6-8 hours and 24 hours after occurrence of the abnormality. If INR is elevated at either timepoint, a subsequent INR assessment should be performed at 72 hours to ensure resolution.

Coagulation (PT/INR/PTT) will be collected for Part A and Part B at the times indicated below:

- Screening
- Pre-infusion on each dosing day
- EoT visit

11.6.2.9.8 Cardiac Troponin and BNP (or NTproBNP)

Blood samples for cardiac troponin and brain natriuretic peptide (BNP) or n-terminal pro b-type natriuretic peptide (NTproBNP) measurements will be collected for Part A and Part B (as specified in Table 16 and Table 17) as follows:

- Screening
- As clinically indicated

Cardiac troponin I is preferred when available, however if not, cardiac troponin T is acceptable. To allow comparison with baseline, sites are requested to maintain consistency with the troponin assay used. Isolated troponin elevations are not sufficient to trigger dosing changes and should be evaluated in the context of other cardiac findings.

If an unscheduled ECG is performed for patient assessment, an electrolyte panel (ie, calcium, magnesium potassium) must be done. If clinically indicated, a troponin assay should coincide with this evaluation including referral to a cardiac specialist.

11.6.2.9.9 Cortisol, ACTH, and TSH

A blood sample for cortisol, adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH) will be collected for Part A and Part B (as specified in Table 16) as follows:

- Screening (between Day -28 and -1)
- Cycle 1 Day 8; pre-infusion
- EoT visit

11.6.2.9.10 Serum Immunoglobulins

Samples for serum immunoglobulins will be collected for Part A and Part B (as specified in Table 16) as follows:

- Screening (between Day -28 and -1)
- Cycle 1 Day 8: pre-infusion
- EoT visit

11.6.2.9.11 Urinalysis

Urinalysis will be performed to assess glucose, protein, blood, ketones, and leucocyte esterase. Results must be available prior to dosing.

Samples for urinalysis will be collected for Part A and Part B at the times indicated below:

- Screening (-28 to -1)
- Pre-infusion on each dosing day
- EoT visit

11.6.2.9.12 Overnight Stays for TLS Monitoring

Overnight stays are recommended on infusion days during Cycle 1, but patients may be discharged prior to 24 hours post-dose, as per Investigator discretion, if their TLS laboratory values are appropriate, and if the patient is able to return for a follow-up clinic visit to complete required safety and laboratory assessments within the specified time windows. Thereafter, dosing as an inpatient will be as per Investigator discretion, based on prior tolerability and risk of TLS.

Tumour lysis syndrome monitoring should be performed (as specified in Table 16) at least twice in the first 24 hours after each administration of study treatment, and thereafter as clinically indicated.

11.6.2.9.13 Clinical and Laboratory Assessments for TLS

The classification of laboratory TLS and clinical TLS is described in Appendix G. Patients will be evaluated for clinical signs and symptoms of TLS during treatment with AZD0466, and blood samples for laboratory assessments will be collected according to the respective module SoA.

Laboratory parameters from the clinical chemistry panel, which are indicative of TLS (according to the Howard modification of Cairo-Bishop criteria, Appendix G), including serum levels of uric acid, potassium, phosphate, calcium, and creatinine, will be evaluated. Blood urea nitrogen and lactate dehydrogenase may also be evaluated to aid assessment. Fluid

balance must be monitored per institutional standards. Blood samples for monitoring TLS will be collected at the timepoints as indicated in Table 16 and as clinically indicated.

Recommended prophylaxis for TLS is outlined in Appendix F.

11.6.2.10 Adverse Events and Serious Adverse Events

Refer to the core protocol (Section 8.3).

11.6.2.10.1 Pregnancy

Refer to the core protocol (Section 8.3.13).

11.6.2.10.2 Medication Error

Refer to the core protocol (Section 8.3.14).

11.6.2.10.3 Overdose

Refer to the core protocol (Section 8.4).

11.6.3 Human Biological Samples

11.6.3.1 Pharmacokinetics

Pharmacokinetic samples may be subjected to further analyses in order to further investigate the presence and/or identity of drug metabolites. These samples will be separate from the primary PK samples sent to the bioanalytical laboratory for analysis. Any results from such analyses will be reported separately from the CSR.

11.6.3.1.1 Urine Pharmacokinetics (in select cohort(s) only)

Samples for PK characterisation and potential analysis of urine metabolites will be collected in a select cohort(s) (based on emerging data) at the following times for Part A only. Note: Collection time begins from start of infusion:

Urine PK

Study period	Day	Timepoint
Cycle 1	Day 1	0-2 hours (+10 min)
		2-6 hours (±15 min)
		6-10 hours (±1 hour)
		10-24 hours (±2 hours)
	Day 2	24-36 hours (±2 hours)
	Day 4	0-2 hours (+10 min)
		2-6 hours (±15 min)
		6-10 hours (±1 hour)
		10-24 hours (±2 hours)
	Day 5	24-36 hours (±2 hours)
	Day 8	0-2 hours (+10 min)
		2-6 hours (±15 min)
		6-10 hours (±1 hour)
		10-24 hours (±2 hours)
	Day 9	24-36 hours (±2 hours)

11.6.3.1.2 Blood Sample for Plasma Pharmacokinetics

Blood samples should be taken from a different part of the body than where the study treatment is being infused, including if central line access is available, to prevent erroneous drug concentration readings. For example, if AZD0466 is being infused into the patient's right arm, then the blood sample should be collected from the left arm.

Blood samples for will be collected at the following times (collection time begins from start of infusion):

Blood Sample for Plasma Pharmacokinetics				
Study period	**Day**	**Timepoint**	**Part A**	**Part B**
Cycle 1	Day 1	Pre-infusion	X	X
		End of the infusion (+10 min)[a]		
	Day 4	Pre-infusion	X	X
		End of the infusion (+10 min)[a]		
	Day 8	Pre-infusion	X	X
		30 min after start of infusion (±5 min)	X	X
		End of the infusion (+10 min)[a]	X	X
		2 hours from start of Day 8 infusion (±15 min)	X	X
		6 hours from start of Day 8 infusion (±30 min)	X	X
		9 hours from start of Day 8 infusion (±1 hour)[b]	X	X
	Day 9	24 hours after the start of the Day 8 infusion (±2 hours)	X	X
	Day 10	48 hours after the start of the Day 8 infusion (±3 hours)	X	X
	Day 11	72 hours after the start of the Day 8 infusion (±7 hours)	X	X
	Day 30/31	At MRD timepoint		X
Cycle 2	Day 1	Pre-infusion	X	X
		End of the infusion (+10 min)[a]	X	X
		2 hours from start of infusion (±15 min)	X	X
		6 hours from start of infusion (±30 min)	X	X
		9 hours from start of infusion (±1 hour)	X	X
	Day 2	24 hours after the start of the Day 1 infusion (±2 hours)	X	X
	Day 23-28	At MRD timepoint		X
Cycle 3 and beyond	Day 1	Pre-infusion	X	X
		End of the infusion (+10 min)[a]	X	X
	Day 23-28	At MRD timepoint		X

Note: Please refer to Section 11.6.2.6 for ECGs measured at all matched PK sample timepoints.

[a] As close as possible to the end of the infusion, but permissible up to 10 minutes.

[b] In the event that a planned collection is no longer possible at the scheduled timepoint, the Medical Monitor must be informed, and any collection outside allotted window must be discussed with the Medical Monitor.

11.6.3.1.3 CCI

CCI

CCI

CCI	CCI	CCI
CCI	CCI	CCI
		CCI
		CCI
		CCI
		CCI
		CCI
CCI	CCI	CCI
		CCI
		CCI
		CCI
		CCI

11.6.3.2 Pharmacodynamics

11.6.3.2.1 CCI

Mandatory whole blood samples will be collected from all patients at the timepoints indicated in the SoA (Table 16 and Table 17) and as shown below. CCI

Note: Collection time begins with the start of infusion.

CCI

[redacted]

11.6.3.2.2 Pharmacodynamic CCI

Mandatory whole blood samples will be collected from all patients at the timepoints indicated in the SoA (Table 16 and Table 17) and as shown below. CCI

[redacted]

Blood for Pharmacodynamic CCI [redacted]

Study period	Day	Ramp-up (RU) or Target Dose (TD)	Timepoint	Part A	Part B
Screening	-	-	-	X	X
Cycle 1	Day 1	RU1 Day 1	Pre-infusion	X	X
			End of infusion (+10 min)	X	X
			6 hours after start of infusion (± 30 min)	X	X
	Day 2	RU1 Day 2	24 hours after start of Day 1 infusion (± 2 hours)	X	-
	Day 4	RU2 Day 1	Pre-infusion	X	X
			End of infusion (+10 min)	X	X
	Day 5	RU2 Day 2	24 hours after start of Day 4 infusion (± 2 hours)	X	-
	Day 8	TD Day 1	Pre-infusion	X	X
			End of infusion (+10 min)	X	X
			6 hours after start of infusion (± 30 min)	X	-
	Day 9	TD Day 2	24 hours after start of Day 8 infusion (± 2 hours)	X	-
Cycle 2	Day 1	-	Pre-infusion	X	-
			6 hours after start of infusion (± 30 min)	X	-
	Day 2	-	24 hours after start of Day 1 infusion (± 2 hours)	X	-
Disease Progression/ End of treatment	-	-	End of treatment	X	X

11.6.3.2.3 Peripheral Blood Smears

Mandatory peripheral blood smears will be collected at the timepoints indicated in the SoA (Table 16 and Table 17) and as shown below to evaluate CCI [redacted] and normal blood cells and detect morphologic apoptotic responses in the blood. Blood smears will be obtained from CBC samples collected for Part A only. Note: Collection time begins with the start of infusion.

Peripheral Blood Smears - Part A Only			
Study period	**Day**	**Ramp-up (RU) or Target Dose (TD)**	**Timepoint**
Screening	-	-	-
Cycle 1	Day 1	RU1 Day 1	Pre-infusion
			End of infusion (+10 min)
	Day 2	RU1 Day 2	24 hours after start of Day 1 infusion (± 2 hours)
	Day 4	RU2 Day 1	Pre-infusion
			End of infusion (+10 min)
	Day 5	RU2 Day 2	24 hours after start of Day 4 infusion (± 2 hours)
	Day 8	TD Day 1	Pre-infusion
			End of infusion (+10 min)
			6 hours after start of infusion (± 30 min)
	Day 9	TD Day 2	24 hours after start of Day 8 infusion (± 2 hours)
Cycle 2	Day 1	-	Pre-infusion
	Day 2	-	24 hours after start of Day 1 infusion (± 2 hours)
Disease Progression/End of treatment	-	-	End of treatment

11.6.4 Human Biological Sample Biomarkers

11.6.4.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study, the patient consents to the mandatory research components of the study.

Samples for biomarker research are required and will be collected from all patients in this study as specified in the SoA (Table 16 and Table 17).

11.6.4.1.1 CCI

CCI [redacted]

CCI

[redacted]

11.6.4.1.2 CCI

CCI

[redacted]

CCI

[redacted]

11.6.4.1.3 CCI

CCI

CCI

11.6.4.1.4 CCI

CCI

CCI

11.6.4.1.5 CCI

CCI

CCI

11.6.4.1.6 Bone Marrow Biopsy and Aspirate CCI

A mandatory pretreatment bone marrow biopsy and aspirate will be required for standard disease profiling and CCI (Section 11.6.1). Bone marrow biopsy samples will be collected in accordance with local/institutional guidelines and as per the process delineated in the laboratory manual. CCI

Mandatory biomarker analysis will be also performed for any bone marrow aspirate and biopsy collected for disease assessment and at disease progression, according to the timepoints in Table 16 and Table 17. Note: The disease progression sample may be taken at the safety follow-up visit if not collected previously.

11.6.4.2 Collection of Optional Biomarker Samples

Refer to the core protocol (Section 8.6.1.1)

11.6.5 Other Study Related Biomarker Research

11.6.5.1 CCI

CCI

CCI .

For storage, re-use, and destruction of biomarker samples see Appendix C.

11.6.6 Optional Genomics Initiative Sample

Refer to the core protocol (Section 8.7).

11.7 STATISTICAL CONSIDERATIONS - MODULE 1

11.7.1 Statistical Hypotheses

No formal statistical hypothesis testing is planned.

11.7.2 Sample Size Determination

11.7.2.1 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 approximately 36 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 66 patients will be enrolled to yield approximately 36 DLT-evaluable patients and 18 patients for further exploration in Part A. This limits the number of patients exposed to AZD0466 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.

11.7.2.2 Part B Monotherapy Dose Expansion

Separate expansion cohorts will enrol 4 distinct populations of patients with advanced haematological malignancies. Three of these expansion cohorts (Expansion Cohorts B1, B2, and B4) will recruit at least 21 patients, and one (Expansion Cohort B3) will recruit at least 25 patients. The total number of patients treated in Part B will be at least 88. These sample sizes have been determined to ensure confidence intervals constructed around the complete response rate (CR+CR_i), as calculated after all patients have had the opportunity to complete one treatment cycle, will provide sufficient information to enable decisions to be made around the likely success of future studies in these patient populations, using methodology described in Frewer et al 2016.

Thresholds for decision making were set for each expansion cohort based on range of literature and expert opinion. For Expansion Cohort B1, a target value for response was set at 35%, with a lower reference value of 20%. If 7 or more responders are observed from 21 patients, there will be at least an 80% chance that the true response rate is at least 20%, which may promote a positive decision. If 4 or fewer responders are observed, then there is a 10% or less chance that the true rate is at least 35%, which may lead to a futility decision. If

the true rate of response is 15%, then, with 21 patients, there is an 80.3% probability of a result that may trigger a decision to stop further development in this population due to futility. This analysis will be performed using the ITT population.

An IA as described in Section 11.7.9 will be performed in each expansion cohort when 12 patients have had the opportunity for one cycle of treatment and is response evaluable as per Table 21. The number of patients is based on the operating characteristics of the cohort-specific decisions using the approach as described in Frewer et al 2016.

In Expansion Cohort B1, if 5 or more responders are observed from 12 patients, then there is at least an 80% chance that the true response rate is at least 20%, which may promote a decision to continue to full recruitment. It may be considered futile to continue development of this cohort if there is < 10% probability for the response rate to be greater than 35%. This translates to observing one or zero responders out of 12 patients.

For the other expansion cohorts, Expansion Cohorts B2, B3, and B4, the target values and lower values for response were set at (40%, 25%), (25%, 13%) and (40%, 25%) respectively. Descriptive statements for these expansion cohorts are given below, with values for the final (and interim) analyses presented using brackets for the IA.

For Expansions Cohorts B2 and B4, a target value for response was set at 40%, with a lower reference value of 25%. In either of these cohorts, if 8 (5) or more responders are observed from 21 (12) patients, there will be at least an 80% chance that the true response rate is at least 25%, which may promote a positive decision. If 5 (1) or fewer responders are observed, then there is a 10% or less chance that the true rate is at least 40%, which may lead to a futility decision. If the true rate of response is 20%, then with 21 (12) patients, there is a 76.9% (55.8%) probability of a result that may trigger a decision to stop further development in these populations for futility.

For Expansion Cohort B3, a target value for response was set at 25%, with a lower reference value of 13%. If 6 (3) or more responders are observed from 25 patients there will be at least an 80% chance that the true response rate is at least 13%, which may promote a positive decision. If 3 (0) or fewer responders are observed, then there is a 10% or less chance that the true rate is at least 25%, which may lead to a futility decision. If the true rate of response is 8%, then with 25 (12) patients, there is an 86.5% (36.7%) probability of a result that may trigger a decision to stop further development in these populations due to futility.

11.7.3 Populations for Analyses

The following populations for analyses are defined in Table 21.

Table 21 Populations for Analysis

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
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 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 DLT evaluation period Or Have experienced a DLT
Pharmacokinetics	Dosed patients with at least one reportable plasma concentrations and no important AEs or protocol deviations that may impact PK

AE, adverse event; DLT, dose-limiting toxicity; PK, pharmacokinetics.

11.7.4 Statistical Analyses

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints specific to this module.

11.7.5 General Considerations

For the dose escalation, Part A, a final analysis will be performed when the MTD has been determined and the last patient to be recruited (including any backfill patients) has had the opportunity to complete 2 cycles of treatment, or has discontinued or withdrawn from treatment. Response and survival data will continue to be collected for ongoing patients until this milestone is reached for the final patient.

For Part B, an IA will be performed when the twelfth patient has had the opportunity to complete one cycle of treatment and is response evaluable as per Table 21. This analysis will include evaluation of clinical response and AEs leading to discontinuation. Provided recruitment is not stopped due to futility or safety concerns, a second IA will be performed once all patients recruited have had the opportunity to complete one cycle of treatment, with efficacy analyses based on the ITT population. The final analysis of the expansion cohorts will be undertaken when either the last patient from all expansion cohorts has had the opportunity to complete 6 months of treatment, or all patients have withdrawn from the study or died. Thereafter, patients who are still on study treatment may remain on treatment and individual patients will continue to be assessed for safety as specified in the protocol.

11.7.6 Efficacy

Part B: Calculation or Derivation of Efficacy Variables

Patients will be assigned a response of CR, CR_i, MLFS, PR, CR_c, CR_m, Relapse or Failure for according to the criteria described in Appendix J for AML or CR, CR_i, Failure, or Relapse according to the criteria in Appendix K for ALL. This is regardless of whether visits were scheduled or unscheduled and also regardless of whether a patient discontinues study intervention or receives another anticancer therapy.

The disease response endpoints ($CR+CR_i$, time to response [TTR], and DoR) will then be derived from the bone marrow biopsy dates and overall visit responses.

Complete response rate is defined as the proportion of patients with a best response of CR or CR_i. Any treated patient who has not satisfied the criteria for CR or CR_i will be treated as a non-responder for this analysis.

Time to response is defined as the time from date of first dose until the date of first documented CR or CR_i. The analysis will include all dosed patients who have a complete response. Patients who go off treatment without a clinical response, receive a subsequent therapy, and then respond will not be included.

Duration of response will be defined as the time from the date of first documented response (CR or CR_i) until date of documented progression, relapse or failure according Appendix J for AML and Appendix K for ALL or death due to any cause. Patients who are not known to have reached one of these endpoints at the time of data cut-off (DCO) will be censored at the last overall response assessment on or before the start of subsequent therapy.

Overall survival is defined as time from date of first dose until the date of death due to any cause. For patients who are alive at the time of DCO, OS will be censored on the last date when patients were known to be alive. Note: Survival calls will be made following the date of DCO for the analysis (these contacts should generally occur within 7 days of the DCO). If patients are confirmed to be alive or if the death date is after the DCO date, then these patients will be censored at the date of DCO.

Analysis Methods

The primary efficacy variable will be the Complete Response Rate ($CR+CR_i$). Complete response rate will be estimated with exact 95% confidence intervals based on the exact binomial distribution. Lower one-sided 80% and upper one-sided 90% limits will also be calculated.

For AML patients, other outcomes such as overall response rate (ORR) (best response of $CR+CR_i$+PR) and Leukaemia Response Rate (best response $CR+CR_i$+PR+MLFS) will be

summarised with two-sided 95% confidence intervals based on the exact binomial distribution.

Changes in platelets, blasts and neutrophils will be summarised over time.

All response outcomes will be listed.

Time to response, DoR, and OS will be analysed using the Kaplan-Meier method. Quartiles, including the median, will be calculated along with 95% confidence intervals as well as rates at 3, 6, 9, and 12 months post first dose.

11.7.7 Safety

There are no module-specific safety analyses planned.

11.7.8 Other Analyses

11.7.8.1 Pharmacokinetics

Calculation or Derivation of Pharmacokinetic Variables

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

Plasma

C_{max}	Maximum observed plasma (peak) drug concentration
t_{max}	Time to reach peak or maximum observed concentration or response following drug administration
λz	Terminal rate constant, estimated by log-linear least squares regression of the terminal part of the concentration-time curve
$t_{1/2}$λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
AUC_{0-72}	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
AUC_{cml}	Area under the plasma concentration-curve from time 0 on Day 1 through the first full dose on Day 8 and extrapolated through infinity.
t_{last}	Time of last observed (quantifiable) concentration
C_{trough}	Concentration prior to dosing
Dose normalised AUC_{last}[a]	Area under the plasma concentration-time curve from time 0 to time of last quantifiable analyte concentration divided by the dose administered
Dose normalised AUC_{0-72}[a]	Area under the plasma concentration-time curve from time 0 to 72 hours after the start of infusion
Dose normalised C_{max}[a]	Maximum observed plasma (peak) drug concentration divided by the dose administered

[a] Calculated for total AZD4320 only

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

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

Urine

Urine PK parameters will be calculated for total AZD4320 including renal clearance and amount excreted unchanged. Plasma and urine data:

Ae_{0-72}	Cumulative amount of unchanged drug excreted into urine from time 0 to 72 hours after the start of infusion
Fe	Percentage of dose excreted unchanged in urine

Ae_{0-72}	Cumulative amount of unchanged drug excreted into urine from time 0 to 72 hours after the start of infusion
CLR	Renal clearance of drug from plasma

Additional PK parameters may be calculated as appropriate.

PK summary statistics

Plasma concentrations of AZD4320 will be summarised by nominal sample time. Plasma concentrations and derived PK parameters will be summarised by dose level and cohort. Plasma concentrations at each timepoint will be summarised according to dose and cohort by the following summary statistics:

- The geometric mean (g_{mean}, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (CV, calculated as 100 √ [exp(s2)-1], where s is the standard deviation of the data on a log scale)
- G_{mean} ± standard deviation (calculated as exp[μ±s])
- Arithmetic mean calculated using untransformed data
- Standard Deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for the estimated PK parameters, as appropriate:

- G_{mean}, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- CV, calculated as 100 √ [exp(s2)-1], where s is the standard deviation of the data on a log scale)
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

The pharmacokinetic data for AZD4320 will also be displayed graphically. Displays will include AZD4320 (total and released) plasma concentration subject profiles (on the linear and log scale) versus time and G_{mean} concentration (±standard deviation) versus time, stratified by

dose.

Scatter plots of PK parameters versus dose, or log-dose, may also be considered to assess dose proportionality.

CCI

CCI

CCI

11.7.9 Interim Analyses

Each cohort in Part B will have an internal IA for futility, with the potential to stop or trigger a combination expansion (to be added via a protocol amendment), followed by a sponsor decision towards further development if the cohort proceeds to full recruitment. During the IA, enrolment may be paused in order to fully evaluate the results. Data for the IA will include all data collected up to the point when the twelfth patient within the cohort has had the opportunity to complete one cycle of treatment with AZD0466 and is response evaluable as per Table 21. The Evaluable for Response population will be used for this analysis. Contingent on the outcome of the IA, recruitment will then continue to full recruitment.

The interim analyses for efficacy will consist of summaries rates of best response ($CR+CR_i$) with one-sided lower 80% and upper 90% exact confidence limits compared to the cohort-specific target response rates as described in Section 11.7.2.

An IA for safety in Part B will take place at the same time as the analysis for efficacy, based on the Safety population. Rates of AEs leading to study treatment discontinuation will be compared to pre-specified criteria to inform a ‘stop’ or ‘consider’ decision. The unacceptable rate of AEs leading to study treatment discontinuation is set at 30%. For example, in 12 patients, one or fewer of these AEs would provide at least an 80% chance that the true rate is not greater than 30%. If 4 or more events are observed in 12 patients at the interim then there will be a lower than 10% chance that the rate is under 15% and the study may be stopped due to safety. If the IA takes place with a number other than 12 patients then the threshold rates of AEs leading to discontinuation may differ from the example provided.

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

11.7.10 Data Monitoring Committee

There will be no DMC for this study. The sponsor in discussion with the SRC (Appendix A 5) in accordance with its charter will be responsible for making recommendations for

dose-escalation or dose de-escalation decisions after each dose level, including decisions on opening cohorts for backfill.

11.8 REFERENCES - MODULE 1

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12 MODULE 2: INVESTIGATION OF DRUG-DRUG INTERACTION BETWEEN AZD0466 AND VORICONAZOLE IN PATIENTS WITH ADVANCED HAEMATOLOGICAL MALIGNANCIES

12.1 BACKGROUND - MODULE 2

12.1.1 Study Treatment

Refer to Section 6 and Section 12.4 for information on AZD0466; further details are provided in the IB.

12.1.1.1 Non-investigational Product –Voriconazole

Voriconazole is a triazole antifungal medication used to treat serious fungal infections (including invasive candidiasis, invasive aspergillosis, and emerging fungal infections) that occur commonly in patients who are immunocompromised. Voriconazole and other azole antifungal agents are substrates and inhibitors of CYP3A isoforms, and are commonly used for prophylaxis and treatment of fungal infections in patients with acute leukaemia.

The safety profile of voriconazole in adults is based on an integrated safety database of more than 2000 subjects (including 1603 adult patients in therapeutic trials) and an additional 270 adults in prophylaxis trials. This represents a heterogeneous population, containing patients with haematological malignancies, patients with HIV infection with oesophageal candidiasis and refractory fungal infections, non-neutropenic patients with candidaemia or aspergillosis, and healthy volunteers. The most commonly reported adverse reactions during treatment with voriconazole were visual impairment, pyrexia, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema, LFT abnormal, respiratory distress, and abdominal pain. The severity of the adverse reactions was generally mild to moderate. No clinically significant differences were seen when the safety data were analysed by age, race, or gender (Voriconazole Prescribing Information).

12.1.2 Nonclinical Information and Correlative Studies

Preclinical studies of AZD4320 indicate that CYP3A4 may have a major role in the metabolic clearance of AZD4320, the active moiety of AZD0466.

12.1.3 Rationale for Module 2

Drug interactions with CYP3A4 can lead to its inhibition, which can increase drug effect, or to its induction, which can decrease the drug effect. Medicines that are potent CYP3A4 inhibitors include azole antifungals such as voriconazole or itraconazole. Preclinical studies of AZD0466 have identified CYP3A4 as likely to have a significant role in the metabolic clearance of AZD4320.

Drugs that act as inducers or inhibitors of CYP3A4 may affect circulating levels of the active moiety AZD4320 and could alter the efficacy or tolerability of study treatment. Use of voriconazole and other azole antifungal agents is prohibited in Module 1 of this study as it is not known whether a DDI exists between AZD0466 and azole antifungal agents. This prohibition restricts the therapeutic options for management of fungal infections in the population of patients enrolled in Module 1.

Module 2 will investigate the safety, PK, and tolerability of AZD0466 when co-administered with voriconazole, a strong inhibitor of CYP3A4. The investigation of a potential DDI between AZD0466 and voriconazole will inform the continuation or removal of restrictions on use of azole antifungal agents in ongoing and future study modules.

12.1.4 Justification for Module 2 Dose

Module 2 will be initiated by the SRC (Appendix A 5) after a tolerated dose of AZD0466 has been determined in Module 1.

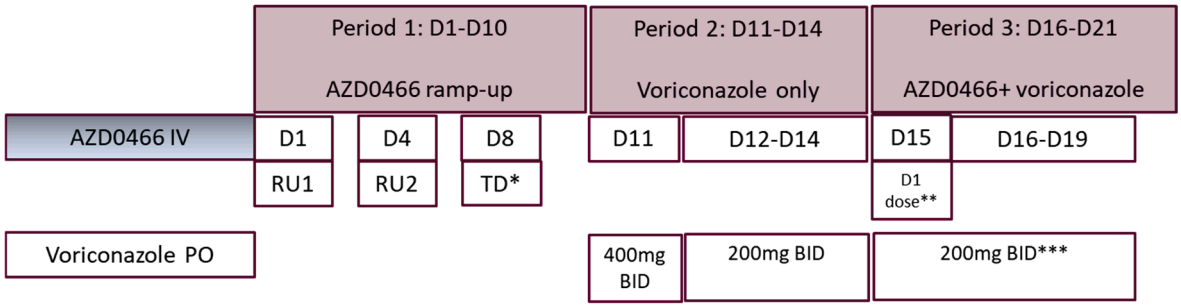
12.1.5 Module 2 Study Design

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 Module 2 Cycle 1 schedule includes Periods 1, 2 and 3. Period 1 involves dose ramp-up in from a starting dose of AZD0466 on Day 1, with subsequent titration to the intermediate dose on Day 4, and to the target dose on Day 8. In Period 2, patients will receive a loading dose of oral voriconazole on Day 11 followed by maintenance dosing on Days 12, 13, and 14, as specified in the prescribing information for voriconazole (Voriconazole Prescribing Information). In Period 3, the dose of AZD0466 administered on Day 15 in combination with voriconazole (at maintenance dose) will be a dose reduction of the target dose (ie, the Day 1 equivalent dose), to mitigate against a potential increase in exposure to the active moiety AZD4320 if a DDI exists between AZD0466 and voriconazole, with a return to the full target dose at the next AZD0466 administration day.

A visual representation of the DDI component of Module 2 (Cycle 1) is shown in Figure 4.

Figure 4 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 (Table 25), 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 on Day 15 (at the Day 1 equivalent dose) 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). 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 Section 11.1.3.1).

Patients who do not wish to continue receiving AZD0466 will undertake the follow-up assessments detailed in Section 7.

Table 22 Module 2 AZD0466 Dose Guidance

AZD0466 Dose*				
Module 2, Cycle 1				Module 2, Cycle 2 and Beyond
D1 RU	D4 RU	D8 TD	D15 (dose equivalent to D1 dose)	D1, D8, D15, D22
75 mg	150 mg	300 mg [a]	75 mg	300 mg weekly [b]
150 mg	300 mg	600 mg [a]	150 mg	600 mg weekly [b]
300 mg	600 mg	1200 mg [a]	300 mg	1200 mg weekly [b]
600 mg	1200 mg	2400 mg [a]	600 mg	2400 mg weekly [b]
1200 mg	2400 mg	3600 mg [a]	1200 mg	3600 mg weekly [b]
2400 mg	3600 mg	5400 mg [a]	2400 mg	5400 mg weekly [b]

[a] Module 2 Cycle 1 will utilise a target dose of AZD0466 that has been declared tolerable in the dose escalation Part A of Module 1.
[b] Patients may receive AZD0466 after Cycle 1 of Module 2 at a higher target dose, without dose ramp up required, if a subsequent AZD0466 dose level has been declared tolerable in Part A of Module 1.
* Doses displayed are for guidance only. Definitive target and ramp-up doses will be decided by the SRC in Module 1 and communicated accordingly.
D, day; RU, ramp up; SRC, Safety Review Committee; TD, target dose.

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.

Overnight stays will be required during Cycle 2 Day 1 and Day 8. Thereafter, dosing as an inpatient will be as per Investigator discretion, based on prior tolerability and risk of TLS.

The SoA for the DDI part (Cycle 1) of Module 2, including PK sampling times, is provided in Section 12.5.1.

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

12.1.6 Benefit-risk Assessment

See Section 2.2 of the core protocol for an overall benefit-risk assessment for AZD0466 in the study population.

Module 2 will utilise a dose of AZD0466 that has been declared tolerable in patients with AML or ALL during the dose escalation Part A of Module 1. With the exception of abnormal LFTs, the most common adverse reactions during treatment with voriconazole do not overlap with the potential risks of treatment with AZD0466. The study protocol incorporates mandatory safety monitoring procedures, including intensive more frequent assessments of

liver biochemistry than for other clinical chemistry parameters, dose modification guidelines, and additional guidance for management of specific AEs.

The available nonclinical and clinical information supports an acceptable benefit-risk assessment for investigation of potential DDI between AZD0466 and voriconazole in patients with advanced haematological malignancies for which there are limited treatment options.

12.2 OBJECTIVES AND ENDPOINTS - MODULE 2

12.2.1 Primary Objectives

See Section 3 of the core protocol.

12.2.2 Secondary Objectives

The secondary objective and endpoint for this module is listed in Table 23. See Section 3 of the core protocol for all other secondary objectives.

Table 23 Secondary Objective – Module 2

Objectives	Endpoints/Variables
Secondary	
• To assess the drug-drug interaction potential between AZD0466 and the azole antifungal voriconazole.	• AUC and C_{max} of AZD4320 after administration of AZD0466 alone and in combination with voriconazole

12.2.3 Exploratory Objectives

See Section 3 of the core protocol for all other exploratory objectives.

12.3 STUDY POPULATION - MODULE 2

Core inclusion and exclusion criteria applicable to all patients enrolled in the study are listed in Section 5.1 and Section 5.2. There are no additional inclusion or exclusion criteria specific to Module 2.

Patients are eligible to be included in the dose escalation part of Module 2 if they meet all of the inclusion criteria in Section 5.1 and none of the exclusion criteria in Sections 5.2. Under no circumstances can there be exceptions to this rule.

Note: Each patient may only be enrolled in one module of this study. A patient who enrols in one module of this study is not eligible to participate in another module.

12.3.1 Inclusion Criteria

Refer to Section 5.1 of the core protocol for the common inclusion criteria applicable to Module 2.

12.3.2 Exclusion Criteria

Refer to the core protocol (Section 5.2). In addition, patients for whom treatment with voriconazole is contraindicated per the local prescribing information must not enter the study.

12.3.3 Lifestyle Considerations

Patients must comply with the restrictions described in the core study protocol (Section 5.3).

12.3.4 Concomitant Medications

Patients must comply with the restrictions described in the core protocol (Section 6.5)

12.3.5 Screen Failures

Refer to the core protocol (Section 5.4).

12.4 Study Treatment - Module 2

Information on the preparation, handling, storage, accountability of study treatment, measures to minimise bias, and study treatment compliance and accountability is either provided in Table 24 and/or referenced in the core protocol (Section 6).

12.4.1 Study Treatment(s) – AZD0466 and Voriconazole

AZD0466 and voriconazole are described in Table 24.

Table 24 Study Treatment for Module 2

Study Treatment	AZD0466	Voriconazole
Dose Formulation	'AZD0466 powder for concentrate for solution for infusion' supplied with 'Solvent for AZD0466 powder for concentrate for solution for infusion'.	Film-coated tablet
Unit Dose Strength(s)	'AZD0466 powder for concentrate for solution for infusion': 500 mg per vial[a] 'Solvent for AZD0466 powder for concentrate for solution for infusion': 20 mL per vial[a]	50 mg, 100 mg, and 200 mg
Dose Level	Dose level of AZD0466 that has been declared tolerable in Module 1 Part A	See Figure 4
Route of Administration	Intravenous	Oral
Dosage preparation and administration	Refer to Handling Instructions	Product should be administered in accordance with the prescribing information.
Provider	AstraZeneca R&D	Provided locally by the study site, subsidiary, or designee[b]
Packaging and Labelling	AZD0466 powder for concentrate for solution for infusion will be provided in 500 mg vials. Each vial will be labelled as per country requirement. Solvent for AZD0466 powder for concentrate for solution for infusion will be provided in 20 mL vials. Each vial will be labelled as per country requirement.	Voriconazole will be provided as a commercial film-coated tablet presentation in a commercial pack.

[a] AZD0466 powder for concentrate for solution for infusion 500 mg/vial is intended to be reconstituted with 20 mL custom solvent to produce AZD0466 concentrate for solution for infusion, 25 mg/mL. If required AZD0466 concentrate for solution for infusion may be further diluted with custom solvent to produce AZD0466 solution for infusion for clinical dosing. Multiple vials of drug product and custom solvent may be used to achieve the required doses.

[b] Under certain circumstances when local sourcing is not feasible treatment may be supplied centrally through AstraZeneca. In the event of central supply voriconazole will be labelled as per country requirement for clinical trial use.

During ramp-up and while patients are considered at risk of TLS, patients must commence oral allopurinol and be encouraged to drink 1.5 to 2 L of fluid at least 24 hours prior to AZD0466 infusion (Appendix F).

Patients will receive study treatment in Cycle 1 of Module 2 as follows:

- Period 1: AZD0466 ramp-up
  Patients will be admitted to hospital and receive a starting ramp-up dose of AZD0466 on Day 1, with subsequent intra-patient ramp-up to an intermediate dose on Day 4, and to the target dose on Day 8. The Day 1 and Day 4 ramp-up doses will be equivalent to those used for that target dose in Module 1.
- Period 2: Voriconazole administration
  Patients will receive voriconazole 400 mg twice daily (BID) on Day 11 and voriconazole 200 mg BID on Day 12-14.
- Period 3: AZD0466 in combination with voriconazole
  Patients will be admitted to hospital and receive AZD0466 on Day 15 at a reduced dose (ie, dose equivalent to the Day 1 dose) and voriconazole 200 mg BID will continue from Day 15 until Day 19. Voriconazole administration on Day 19 will not continue beyond the time of last PK sample collection.

Voriconazole tablets should be taken at least one hour before or one hour after a meal, on each of the voriconazole dosing days.

Patients who continue to receive AZD0466 in Cycle 2 may receive AZD0466 at a higher target dose if a new higher dose level was declared tolerable in the dose escalation part of Module 1. Cycle 2 and subsequent cycles are 28 days in duration in which AZD0466 is administered once weekly on Days 1, 8, 15, and 22 of each cycle. All patients will be treated until progressive disease, unacceptable toxicity or withdrawal of consent.

12.4.2 Preparation, Handling, Storage, and Accountability of Study Treatment

Refer to the core protocol (Section 6.2) for AZD0466. Voriconazole should be stored according to the storage conditions indicated on the product label.

12.4.3 Measures to Minimise Bias

Refer to the core protocol (Section 6.3).

12.4.4 Study Treatment Compliance

Refer to the core protocol (Section 6.4).

12.4.5 Intervention After the End of the Study

Refer to the core protocol (Section 6.8).

12.5 STUDY PLAN AND TIMING OF PROCEDURES – MODULE 2

12.5.1 Schedule of Activities

The SoA for Periods 1, 2, and 3 (Cycle 1) and for subsequent cycles are shown in Table 25 and Table 26.

Table 25 Module 2 - Schedule of Activities for Screening and Cycle 1

Procedure	Screening	Cycle 1 (21 days)																Details in CSP Section or Appendix
		Period 1 AZD0466[a]										Period 2 Voriconazole	Period 3 AZD0466 + Voriconazole					
Day	-28 to -1	1	2	3	4	5	6	7	8	9	10	11-14	15	16	17	18	19	
Informed consent	X																	Appendix A 3
Inclusion and exclusion criteria	X																	5.1; 5.2; 12.3.1; 12.3.2
Demography	X																	8
Medical history	X																	8
Physical examination	X	X	X		X	X			X	X			X	X				12.6.2.1
Height	X																	12.6.2.3
Weight	X	X							X				X					12.6.2.3
Vital signs[b]	X	X*	X	X	X*				X*				X*	X	X	X	X	12.6.2.5
Chest X-ray[c]	X																	12.6.2.4
ECOG performance status	X	X																12.6.2.7
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	12.3.4
Adverse events (AE)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
CCI [redacted]	[redacted]																	[redacted]
Safety ECG (triplicate)	X	X*	X		X*	X			X*	X			X*	X	X	X		12.6.2.6
Cardiac MUGA/MRI/ECHO[d]	X																	12.6.2.7
Laboratory Tests																		
COVID-19 test	X																	12.6.2.9.1

Table 25 Module 2 - Schedule of Activities for Screening and Cycle 1

Procedure	Screening	Cycle 1 (21 days)																Details in CSP Section or Appendix
		Period 1 AZD0466[a]										Period 2 Voriconazole	Period 3 AZD0466 + Voriconazole					
Day	-28 to -1	1	2	3	4	5	6	7	8	9	10	11-14	15	16	17	18	19	
Hepatitis B and C, HIV and CMV	X																	12.6.2.9.2
Pregnancy test (WOCBP only)	X	X																12.6.2.9.3
CBC with differential (CCI [redacted])[e]	X	X*	X		X*	X			X*	X			X*	X				12.6.2.9.6
Clinical chemistry	X	X	X		X	X			X	X			X	X				12.6.2.9.4
TLS monitoring[f]		X*	X*		X*	X*			X*	X*			X*	X*				12.6.2.9.12 and 12.6.2.9.13
CPK	X	X	X		X	X			X	X			X	X				12.6.2.9.4
Coagulation indices	X	X			X				X				X					12.6.2.9.7
Cardiac troponin I[g]	X																	12.6.2.9.8
BNP (or NTproBNP)	X																	12.6.2.9.8
Cortisol, ACTH, TSH	X								X									12.6.2.9.9
Amylase and lipase	X	X			X				X				X					12.6.2.9.5
Serum immunoglobulins	X								X									12.6.2.9.10
Urinalysis	X	X			X				X				X					12.6.2.9.11
CCI [redacted]		[redacted]																[redacted]
Overnight inpatient stay[h]		X			X				X				X					12.6.2.9.12
Administer AZD0466		X			X				X				X					6.1 and 12.1.5

Table 25 Module 2 - Schedule of Activities for Screening and Cycle 1

Procedure	Screening	Cycle 1 (21 days)																Details in CSP Section or Appendix
		Period 1 AZD0466[a]										Period 2 Voriconazole	Period 3 AZD0466 + Voriconazole					
Day	-28 to -1	1	2	3	4	5	6	7	8	9	10	11-14	15	16	17	18	19	
Administer voriconazole												X	X	X	X	X	X	12.4.1
Pharmacokinetic Assessments																		
Blood sample for plasma PK		X*	X	X	X*				X*				X*	X	X	X	X	12.6.3.1
Pharmacodynamic Assessments																		
CCI [redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]			[redacted]	[redacted]			[redacted]	[redacted]				[redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]			[redacted]	[redacted]			[redacted]	[redacted]				[redacted]
Blood for peripheral blood smears	X	X*	X		X*	X			X*	X			X*	X				12.6.1
CCI [redacted]																		
CCI [redacted]	[redacted]																	[redacted]
CCI [redacted]	[redacted]	[redacted]																[redacted]
Disease Assessment																		
Mandatory bone marrow biopsy and aspirate for disease assessment CCI [redacted]	X[i]																	12.6.1; CCI [redacted]
CT/MRI/PET scans (only if extramedullary disease)	X																	8.1.1

[a] Any visits (eg, Day 6 and Day 7) that do not require attendance at the site for blood draw or physical examination can be conducted by telephone, at the Investigator's discretion.
[b] On PK sampling days, blood pressure readings to be taken at each PK sample timepoint. All blood pressure readings can be taken ± 10 minutes from the designated PK sample collection.
[c] Chest X-rays may also be performed at other timepoints during the study at the Investigator's discretion, when clinically indicated.
[d] Cardiac MUGA/MRI/ECHO to assess left ventricular ejection fraction will be conducted. Ensure the same modality is used for each patient. Unscheduled assessment if deemed clinically warranted.
[e] CCI .
[f] At least twice in the first 24 hours after each administration of AZD0466, and as clinically indicated thereafter as per institutional protocol.
[g] Cardiac troponin to be collected at screening (baseline) and at other timepoints in the study, as clinically indicated. Cardiac troponin I is preferred if available, if not, cardiac troponin T is acceptable. To allow comparison with baseline, sites are requested to maintain consistency with the troponin assay used.
[h] Additional inpatient admission days at Investigator discretion.
[i] To be collected at screening between Day -28 and -1. When it is not possible to obtain a new bone marrow biopsy, a historic bone marrow biopsy sample may be used if collected within 28 days of first dose of AZD0466, but a historic bone marrow biopsy sample collected within 14 days of the first dose is preferred.

*Indicates more than one assessment is to be performed at the visit.
ACTH, adrenocorticotropic hormone; AE, Adverse event; BNP, brain natriuretic peptide; CBC, complete blood count; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; CPK, creatine phosphokinase; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; MUGA, multigated acquisition; CCI ; PET, positron emission tomography; PK, pharmacokinetic; TSH, thyroid stimulating hormone; TLS, tumour lysis syndrome; WOCBP, women of childbearing potential.

Table 26 Module 2 - Schedule of Activities for Cycle 2 and beyond

Procedure	Cycle 2				Cycle 3 onwards (28-day cycles)					Follow-up			Details in CSP Section or Appendix
										EoT	Post treatment follow-up[a]	Survival follow-up	
Day	1	2	8/15/22	9/16/23	1	2	8	9/16/23	15/22		28 days after last dose	Every 1 month after last dose	
Visit window	±2 days									±7 days	±7 days	±14 days	
Physical examination	X	X	X	X	X	X	X	X	X	X			12.6.2.1
Weight	X		D15		X				D15	X			12.6.2.3

Table 26 Module 2 - Schedule of Activities for Cycle 2 and beyond

Procedure	Cycle 2				Cycle 3 onwards (28-day cycles)					Follow-up			Details in CSP Section or Appendix
										EoT	Post treatment follow-up[a]	Survival follow-up	
Day	**1**	**2**	**8/15/22**	**9/16/23**	**1**	**2**	**8**	**9/16/23**	**15/22**		**28 days after last dose**	**Every 1 month after last dose**	
Visit window	**±2 days**									**±7 days**	**±7 days**	**±14 days**	
Vital signs[b]	X*	X	X*	D9	X*		X*	Every disease assessment in (D23-D28)	X*	X			12.6.2.5
ECOG performance status	X				X					X			12.6.2.8
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X		12.3.4
Adverse events	X	X	X	X	X	X	X	X	X	X	X		8.3
Safety ECG (Triplicate)	X*	X	D8*	D9	X* (even cycles only from C4)					X			12.6.2.6
Cardiac MUGA/MRI/ECHO[c]			D8				Every 3 Cycles from C5			X			12.6.2.7
Laboratory Tests													
COVID-19 test	X				X					X			12.6.2.9.1
Pregnancy test (WOCBP only)	X				X					X			12.6.2.9.3

Table 26 Module 2 - Schedule of Activities for Cycle 2 and beyond

Procedure	Cycle 2				Cycle 3 onwards (28-day cycles)					Follow-up			Details in CSP Section or Appendix
										EoT	Post treatment follow-up[a]	Survival follow-up	
Day	1	2	8/15/22	9/16/23	1	2	8	9/16/23	15/22		28 days after last dose	Every 1 month after last dose	
Visit window	±2 days									±7 days	±7 days	±14 days	
CBC with differential [redacted][d]	X	X	X	X[e]	X	X	X	X[e]	X	X			12.6.2.9.6
Clinical chemistry	X	X	X	X	X	X	X	X	X	X			12.6.2.9.4
TLS monitoring[f]	X*	X*	D8*	D9*									12.6.2.9.12 and 12.6.2.9.13
CPK	X	X	X	X	X	X	X	X	X	X			12.6.2.9.4
Coagulation indices	X		X		X		X		X	X			12.6.2.9.7
Cortisol, ACTH and TSH										X			12.6.2.9.9
Amylase and lipase	X		X		X		X		X	X			12.6.2.9.5
Serum immunoglobulins										X			12.6.2.9.10
Urinalysis	X		X		X		X		X	X			12.6.2.9.11
Overnight inpatient stay	X		D8										12.6.2.9.12
Administer AZD0466	X		X		X		X		X				6.1

Table 26 Module 2 - Schedule of Activities for Cycle 2 and beyond

Procedure	Cycle 2				Cycle 3 onwards (28-day cycles)					Follow-up			Details in CSP Section or Appendix
										EoT	Post treatment follow-up[a]	Survival follow-up	
Day	**1**	**2**	**8/15/22**	**9/16/23**	**1**	**2**	**8**	**9/16/23**	**15/22**		**28 days after last dose**	**Every 1 month after last dose**	
Visit window	**±2 days**									**±7 days**	**±7 days**	**±14 days**	
Pharmacokinetic assessments													
Blood sample for plasma PK	X*				X*								12.6.3.1.1
Pharmacodynamic assessments													
CCI [redacted]	[redacted]	[redacted]			[redacted]	[redacted]				[redacted]			[redacted]
Blood for pharmacodynamic CCI [redacted]	X	X								X			12.6.3.2.2
Blood for peripheral blood smears	X	X								X			12.6.1

Table 26 Module 2 - Schedule of Activities for Cycle 2 and beyond

Procedure	Cycle 2				Cycle 3 onwards (28-day cycles)					Follow-up			Details in CSP Section or Appendix
										EoT	Post treatment follow-up[a]	Survival follow-up	
Day	1	2	8/15/22	9/16/23	1	2	8	9/16/23	15/22		28 days after last dose	Every 1 month after last dose	
Visit window	±2 days									±7 days	±7 days	±14 days	
CCI													
								CCI					
CCI													
Disease Assessment													
Mandatory bone marrow biopsy and aspirate for disease assessment CCI [g]				D16-17				D23-28		X			12.6.1; 12.6.4.1.3
CT/MRI/PET scans (only if extramedullary disease)								D23-28, C3 and every 3 cycles		X			8.1.1
Survival follow up												X	8

[a] Patients will be followed during the off-treatment period until all treatment related toxicity resolves, or for at least 28 days post-study drug discontinuation or until new therapy. This can be done via telephone contact at the Investigator's discretion.

[b] On PK sampling days, blood pressure readings to be taken at each PK sample timepoint. All blood pressure readings can be taken ± 10 minutes from the designated PK sample collection.
[c] Cardiac MUGA/MRI/ECHO to assess left ventricular ejection fraction will be conducted. Ensure the same modality is used for each patient. Unscheduled assessment if deemed clinically warranted.
[d] Part of collection to be used for peripheral blood smears.
[e] If disease assessment is not on Day 23, an additional CBC sample is required.
[f] At least twice in the first 24 hours after each administration of AZD0466, and as clinically indicated thereafter as per institutional protocol.
[g] To be taken at Cycle 2 Day 16 or 17 and Cycle 3 Day 23-28 or as clinically indicated. If bone marrow is performed on day of infusion must be at least 6 hours post-infusion.

*Indicates more than one assessment is to be performed at the visit.
ACTH, adrenocorticotropic hormone; AE, Adverse event; C, cycle; CBC, complete blood count; COVID-19, coronavirus disease 2019; CPK, creatine phosphokinase; D, Day; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EoT, end of treatment; INR, international normalised ratio; MRI, magnetic resonance imaging; MUGA, multigated acquisition; CCI [redacted]; PET, positron emission tomography; PK, pharmacokinetic; PT, prothrombin time; PTT, partial thromboplastin time; TSH, thyroid stimulating hormone; TLS, tumour lysis syndrome; WOCBP, women of childbearing potential.

12.6 STUDY ASSESSMENTS AND PROCEDURES - MODULE 2

Study procedures and their timings for this module are summarised in the SoA (Section 12.5.1). Patient demographic characteristics, medical history and disease characteristics will be recorded as described in Section 8, Enrolment and Screening.

12.6.1 Efficacy Assessments

12.6.1.1 Peripheral Blood

Peripheral blood will be collected for CBC (laboratory safety assessment) as indicated in the SoA (Table 25 and Table 26). [redacted]

12.6.1.2 Extramedullary Disease

Refer to the core protocol (Section 8.1.1) for details on disease assessment for extramedullary disease.

12.6.1.3 Bone Marrow

Bone marrow core biopsy and bone marrow aspirate should be performed (as indicated in Table 25 and Table 26) as below. Mandatory biomarker analysis (Section 12.6.4.1.3) will be performed any time a bone marrow analysis is performed. If a bone marrow aspirate and biopsy is performed on a dosing day, it must be at least 6 hours post infusion. In Module 2, in the event that a patient is otherwise eligible but extenuating circumstances preclude obtaining a new on-study bone marrow biopsy, a historic bone marrow biopsy sample may be used if collected within 28 days of first dose, but within 14 days is preferred, with the approval of the Medical Monitor.

- 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.

12.6.1.4 Survival Follow-up

Refer to the core protocol (Section 8, Follow-up Period).

12.6.2 Safety Assessments

12.6.2.1 Physical Examination

A complete physical examination will be performed and include assessments of the following: general appearance, abdomen, skin, head, and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, respiratory, cardiovascular, musculoskeletal (including spine and extremities), and neurological systems. Investigators should pay special attention to clinical signs related to previous serious illnesses. New or worsening abnormalities may qualify as AEs (see Section 8.3.5 for details). Targeted physical examinations will be performed throughout the treatment period, at the discretion of the Investigator eg, for new or worsening symptoms and/or signs.

Physical examinations should be performed (as specified in the SoA in Table 25 and Table 26) as follows:

- Screening
- Cycle 1 Period 1 and Period 3: pre-infusion on each dosing day
- Cycle 1 Period 1 and Period 3: 24 hours after each infusion
- Cycle 2 and beyond: pre-infusion on each dosing day
- Cycle 2 and beyond: 24 hours after each infusion
- EoT visit

12.6.2.2 Medical history

Refer to the core protocol (Section 8, Enrolment and Screening).

12.6.2.3 Height and Body Weight

Height will be recorded at screening.

Body weight will be assessed (as specified in the SoA in Table 25 and Table 26) as follows:

- Screening
- Cycle 1 Day 1, 8, and 15: pre-infusion
- Each Cycle thereafter Day 1 and Day 15: pre-infusion
- EoT visit

12.6.2.4 Chest X-ray

Chest x-ray will be performed at screening to provide a baseline against which potential treatment-emergent lung abnormalities may be evaluated. Chest x-rays may also be performed at other timepoints during the study at the Investigator's discretion, when clinically indicated.

12.6.2.5 Vital Signs

Vital signs will include heart rate, pulse, systolic and diastolic BP, respiration rate, height (at screening), and temporal temperature. Blood pressure and pulse measurements will be assessed in a seated or semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available. Measurements should be preceded by at least 10 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).

On PK sampling days, BP readings to be taken at each PK sample timepoint. All BP readings can be taken ±10 minutes from the designated PK sample collection.

Vital signs should be assessed (as specified in the SoA in Table 25 and Table 26) as follows:

- Screening
- Cycle 1 Period 1, Day 1: pre-infusion, 30 minutes (±5 minutes) after the start of the infusion, at the end of the infusion (+10 minutes), and 2 hours (±15 minutes), 6 hours (±30 minutes), 9 hours (±1 hour) after the start of the infusion
- Cycle 1 Period 1, Day 2: 24 hours (±2 hours) after the start of the Day 1 infusion
- Cycle 1 Period 1, Day 3: 48 hours (±3 hours) after the start of the Day 1 infusion
- Cycle 1 Period 1, Day 4: 72 hours after the start of the Day 1 infusion (up to 3 hours before Day 4 infusion), 30 minutes (±5 minutes) after the start of the infusion, and at the end of the infusion (+10 minutes)
- Cycle 1 Period 1, Day 8: pre-infusion, 30 minutes (±5 minutes) after the start of the infusion, and at the end of the infusion (+10 minutes)
- Cycle 1 Period 3, Day 15: pre-infusion, 30 minutes (±5 minutes) after the start of the infusion, at the end of the infusion (+10 minutes), and 2 hours (±15 minutes), 6 hours (±30 minutes), 9 hours (±1 hour) after the start of the infusion
- Cycle 1 Period 3, Day 16: 24 hours (±2 hours) after the start of the Day 15 infusion
- Cycle 1 Period 3, Day 17: 48 hours (±3 hours) after the start of the Day 15 infusion
- Cycle 1 Period 3, Day 18: 72 hours (±3 hours) after the start of the Day 15 infusion
- Cycle 1 Period 3, Day 19: 96 hours (±3 hours) after the start of the Day 15 infusion
- Cycle 2 Day 1: pre-infusion, 30 minutes (±5 minutes) after the start of the infusion, and at the end of the infusion (+10 minutes)
- Cycle 2 Day 2: 24 hours (±2 hours) after the start of the Day 1 infusion
- Cycle 2 Day 8: pre-infusion, 30 minutes (±5 minutes) after the start of the infusion, and at the end of the infusion (+10 minutes)
- Cycle 2 Day 9: 24 hours (±2 hours) after the start of the Day 8 infusion

- Cycle 2 Day 15: pre-infusion, 30 minutes (±5 minutes) after the start of the infusion, and at the end of the infusion (+10 minutes)
- Cycle 2 Day 16 or 17: at time of disease assessment
- Cycle 2 Day 22: pre-infusion, 30 minutes (±5 minutes) after the start of the infusion, and at the end of the infusion (+10 minutes)
- Cycle 3 and beyond Day 1, 8, 15 and 22: pre-infusion, 30 minutes (±5 minutes) after the start of the infusion, and at the end of the infusion (+10 minutes)
- At each cycle: at time of disease assessment
- EoT visit

12.6.2.6 Electrocardiograms

Digital 12-lead ECGs (triplicate ECGs, all 3 within a 5-minute time period) will be obtained after the patient has been resting in a supine position for at least 10 minutes. ECGs will be measured before vital signs and prior to PK blood draws at all matched PK sample timepoints. A standardised ECG machine provided by the central ECG vendor should be used and the patient should be examined using the same machine throughout the study, where feasible.

If an unscheduled ECG is done at any time, then an electrolyte panel (Section 12.6.2.9) must be collected to coincide with ECG testing.

Central ECG reads will be utilised during this study. Standard ECG parameters to be determined will include HR/RR, PR, QRS, QT and QTcF (QT interval corrected for HR using Fridericia's formula) intervals.

After the ECGs have been recorded, the Investigator or designated physician will review each of the ECGs at all timepoints for the presence of abnormalities (including rhythm, ECG intervals, or repolarisation abnormalities) and may refer to a local cardiologist if appropriate. A paper copy of the ECG should be filed in the patient's medical records. For all ECGs, an overall evaluation and interpretation should be recorded by the Investigator or designated physician. Any clinically significant abnormalities detected require a confirmatory ECG. In case that the centrally provided ECG machine is unavailable or technical issues occur that preclude correct measurement, local ECGs (using the site owned device) may be performed instead.

See Section 6.6.5 for management of cardiac findings and cardiovascular parameters that require treatment to be withheld or increased monitoring. Twelve-lead centrally-read digital ECGs will be performed in triplicate; collection times are from the start of AZD0466 infusion.

ECGs should be performed as specified in the SoA Table 25 and Table 26, and Table 27.

Table 27 PK Timepoints and Corresponding Safety ECG Timepoints (Module 2)

Study period		Day	Timepoint	Triplicate Safety ECGs
Screening		-28 to -1	Baseline	X
Cycle 1	Period 1	1	Pre-infusion	X[a]
			End of the infusion (+10 min)	X[a]
		2	24 hours after the start of the Day 1 infusion (±2hours)	X[a]
		4	Pre-infusion	X[a]
			End of the infusion (+10 min)	X[a]
		5	24 hours after the start of the Day 4 infusion (±2 hours)	X
		8	Pre-infusion	X[a]
			End of the infusion (+10 min)	X[a]
		9	24 hours after the start of the Day 8 infusion (±2 hours)	X
	Period 3	15	Pre-infusion	X[a]
			End of the infusion (+10 min)	X[a]
		16	24 hours after the start of the Day 15 infusion (±2hours)	X[a]
		17	48 hours after the start of the Day 15 infusion (±2hours)	X[a]
		18	72 hours after the start of the Day 15 infusion (±2 hours)	X[a]
Cycle 2		1	Pre-infusion	X[a]
			End of the infusion (+10 min)	X[a]
		2	24 hours after the start of the Cycle 2 Day 1 infusion (±2 hours)	X
		8	Pre-infusion	X
			End of the infusion (+10 min)	X
		9	24 hours after the start of the Cycle 2 Day 8 infusion (±2 hours)	X
Cycle 4 and even cycles thereafter		1	Pre-infusion	X[a,b]
			End of the infusion (+10 min)	X[a,b]
End of Treatment				X

[a] At PK sampling visits, triplicate ECGs will be collected before the PK sample is taken (please refer to Section 12.6.3.1.1 for additional PK assessments).

[b] Beyond Cycle 2 ECGs will be collected on Day 1 of even cycles only, ie, Cycle 4, 6, 8 etc: pre-infusion and at the end of the infusion (+10 minutes).

12.6.2.7 Cardiac MUGA/MRI/ECHO

A cardiac MUGA/ MRI/ECHO to assess LVEF will be conducted. The modality of the cardiac function assessments must be consistent within a patient ie, if ECHO is used for the screening assessment then ECHO should also be conducted at subsequent assessments. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study treatment, to confirm reversibility of the abnormality. The patients should also be examined using the same machine and operator whenever possible.

Unscheduled assessments should be performed as clinically indicated, including after a clinically significant ECG finding (T wave inversion/flattening, significant QRS amplitude changes or symptomatic patient, etc). In case of any T wave abnormality, the ECHO, MRI, or MUGA should be repeated at the EoT visit to address the question of recovery during the off-treatment period.

Cardiac MUGA/MRI/ECHO should be performed at the times specified in the SoA (Table 25 and Table 26) as follows:

- Screening
- Cycle 2, Day 8
- Every 3 cycles from Cycle 5 (ie, Cycle 5, 8, 11, etc), Day 8
- EoT visit

12.6.2.8 Performance Status

ECOG performance status (Appendix L) will be assessed at the times specified in the SoA (Table 25 and Table 26) as follows.

- Screening
- Every Cycle Day 1
- EoT visit

12.6.2.9 Clinical Safety Laboratory Assessments

Clinical laboratory safety tests, including urine or serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

Laboratory values will be repeated/confirmed and followed up as appropriate.

Safety laboratory assessments will be performed at the timepoints specified in the SoA (Table 25 and Table 26). Additional sampling times may be added or removed if indicated by the emerging data.

12.6.2.9.1 COVID-19 Testing

COVID-19 tests will be conducted where appropriate and in accordance with local procedures. COVID-19 testing, may include nucleic acid/PCR and/or serological approaches. This should be performed as follows:

- Screening: patients with a positive PCR test, must be antigen negative with confirmed IgG antibodies to COVID-19 to be able to start treatment
- At each cycle from Cycle 2 onwards Day 1: pre-infusion
- EoT visit

12.6.2.9.2 Viral Serology

A Hepatitis B, Hepatitis C, HIV and CMV viral serology sample will be collected at screening. If a patient was found to have positive anti-HBc antibody and a negative HBsAg, a DNA PCR test will be done to determine eligibility criteria.

12.6.2.9.3 Pregnancy Test (Women of Childbearing Potential Only)

A urine/serum sample for a pregnancy test will be collected from all women of childbearing potential (defined in Section 5.3) as follows:

- Screening
- Day 1 of each cycle: pre-infusion
- EoT visit

12.6.2.9.4 Clinical Chemistry

Blood samples for determination of clinical chemistry will be collected as specified in Table 25 and Table 26. Unscheduled samples may be collected if deemed clinically warranted, and results of unscheduled assessment should be recorded in the eCRF.

If an unscheduled ECG is performed for patient assessment, an electrolyte panel (ie, calcium, magnesium potassium) must be done. If clinically indicated, a troponin assay should coincide with this evaluation. Cardiac troponin I is preferred when available, however if not, cardiac troponin T is acceptable. To allow comparison with baseline, sites are requested to maintain consistency with the troponin assay used. Isolated troponin elevations are not sufficient to trigger dosing changes and should be evaluated in the context of other cardiac findings.

The following clinical chemistry tests will be performed (Table 28).

Table 28 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[b]	Total protein
Bilirubin (total and direct)	Lactate dehydrogenase	Chloride
Blood urea nitrogen	Lipase[c]	Uric acid
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] Glutamate dehydrogenase testing is optional, but should be performed where sites have the capability to perform the test locally.
[c] Collected at screening, pre-infusion on each dosing day, and end of treatment visit.
NB. Refer to Appendix E if alanine amino transferase or aspartate aminotransferase ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN.
ULN, upper limit of normal range.

Results for LFTs must be available and reviewed before each infusion of study treatment throughout Cycle 1 and review of results is recommended before each infusion of study treatment from Cycle 2 and beyond. Values must have returned to the patient's baseline before infusion of AZD0466.

Clinical chemistry, including creatine phosphokinase, should be performed according to the schedule below (collection time begins from start of infusion).

- Screening
- Cycle 1 Period 1 and Period 3: Pre-infusion on each dosing day
- Cycle 1 Period 1 and Period 3: 24 hours (±2 hours) after each dosing
- At each cycle from Cycle 2 onwards: Pre-infusion on each dosing day
- At each cycle from Cycle 2 onwards: 24 hours (±2 hours) after each dosing
- EoT visit

12.6.2.9.5 Amylase and Lipase

Amylase and lipase will be collected according to the schedule below.

- Screening
- Pre-infusion on each dosing day

- EoT visit

12.6.2.9.6 Complete Blood Count with Differential CCI

Complete blood counts with differential CCI (Table 29) will be collected. Part of the blood sample collected for CBC will be used for peripheral blood smears as detailed in Section 12.6.1.

Table 29 Haematology Assessments

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

Collection times are indicated below (collection time begins from start of infusion).

- Screening
- Cycle 1 Period 1, Day 1: pre-infusion, at the end of the infusion (+10 minutes), and 6 hours (±30 minutes) after the start of the infusion
- Cycle 1 Period 1, Day 2: 24 hours (±2 hours) after the start of the Day 1 infusion
- Cycle 1 Period 1, Day 4: pre-infusion and at the end of the infusion (+10 minutes)
- Cycle 1 Period 1, Day 5: 24 hours (±2 hours) after the start of the Day 1 infusion
- Cycle 1 Period 1, Day 8: pre-infusion, at the end of the infusion (+10 minutes), and 2 hours (±30 minutes), 6 hours (±30 minutes) and 9 hours (±1 hour) after the start of infusion
- Cycle 1 Period 1, Day 9: 24 hours (±2 hours) after the start of the Day 8 infusion
- Cycle 1 Period 3, Day 15: pre-infusion, at the end of the infusion (+10 minutes), and 2 hours (±30 minutes), 6 hours (±30 minutes) and 9 hours (±1 hour) after the start of infusion
- Cycle 1 Period 3, Day 16: 24 hours (±2 hours) after the start of the Day 15 infusion
- At each cycle from Cycle 2 onwards: Pre-infusion on each dosing day
- At each cycle from Cycle 2 onwards: 24 hours (±2 hours) after each dosing
- At each disease assessment
- EoT visit

12.6.2.9.7 Coagulation Indices

Prothrombin, INR and PTT will be collected as specified in the individual modules. International normalised ratio assessment should be repeated if any abnormalities above ULN

in liver biochemistry occur, at 6-8 hours and 24 hours after occurrence of the abnormality. If INR is elevated at either timepoint, a subsequent INR assessment should be performed at 72 hours to ensure resolution.

Coagulation (PT/INR/PTT) will be collected at the times indicated below:

- Screening
- Pre-infusion on each dosing day

12.6.2.9.8 Cardiac Troponin and BNP (or NTproBNP)

Blood samples for cardiac troponin and BNP or NTproBNP measurements will be collected (as specified in Table 25 and Table 26) as follows:

- Screening
- As clinically indicated

Cardiac troponin I is preferred when available, however if not, cardiac troponin T is acceptable. To allow comparison with baseline, sites are requested to maintain consistency with the troponin assay used. Isolated troponin elevations are not sufficient to trigger dosing changes and should be evaluated in the context of other cardiac findings.

If an unscheduled ECG is performed for patient assessment, an electrolyte panel (ie, calcium, magnesium potassium) must be done. If clinically indicated, a troponin assay should coincide with this evaluation including referral to a cardiac specialist.

12.6.2.9.9 Cortisol, ACTH, and TSH

Cortisol, ACTH, and TSH will be collected (as specified in Table 25 and Table 26) as follows:

- Screening (between Day -28 and -1)
- Cycle 1 Period 1, Day 8: pre-infusion
- EoT visit

12.6.2.9.10 Serum Immunoglobulins

Samples for serum immunoglobulins will be collected (as specified in Table 25) as follows:

- Screening (between Day -28 and -1)
- Cycle 1 Period 1, Day 8: pre-infusion
- EoT visit

12.6.2.9.11 Urinalysis

Urinalysis will be performed to assess glucose, protein, blood, ketones, and leucocyte esterase. Results must be available prior to dosing.

Samples for urinalysis will be collected at the times indicated below:

- Screening (between Day -28 and -1)
- Pre-infusion on each dosing day
- EoT visit

12.6.2.9.12 Overnight Stays for TLS Monitoring

During Cycle 1 Period 1, study treatment will be administered on an inpatient basis on Day 1, Day 4 and Day 8 to allow TLS monitoring and PK assessments. Overnight stays are also recommended for dosing on Day 15 during Cycle 1 Period 3 and during Cycle 2 for Days 1 and 8, but patients may be discharged prior to 36 hours post-dose as per Investigator discretion, if their TLS laboratory values are appropriate, and if the patient is able to return for a follow-up clinic visit to complete the required safety and laboratory assessments. Thereafter, dosing as an inpatient will be as per Investigator discretion, based on prior tolerability and risk of TLS.

Tumour lysis syndrome monitoring should be performed (as specified in Table 25 and Table 26) at least twice in the first 24 hours after each administration of study treatment, and thereafter as clinically indicated.

12.6.2.9.13 Clinical and Laboratory Assessments for TLS

The classification of laboratory TLS and clinical TLS is described in Appendix G. Patients will be evaluated for clinical signs and symptoms of TLS during treatment with AZD0466, and blood samples for laboratory assessments will be collected according to the respective module SoA.

Laboratory parameters from the clinical chemistry panel, which are indicative of TLS (according to the Howard modification of Cairo-Bishop criteria, Appendix G), including serum levels of uric acid, potassium, phosphate, calcium, and creatinine, will be evaluated. Blood urea nitrogen and lactate dehydrogenase may also be evaluated to aid assessment. Fluid balance must be monitored per institutional standards. Blood samples for monitoring TLS will be collected at the timepoints as indicated in Table 25 and Table 26 and as clinically indicated.

Recommended prophylaxis for TLS is outlined in Appendix F.

12.6.2.10 Adverse Events and Serious Adverse Events

Refer to the core protocol (Section 8.3).

12.6.2.10.1 Pregnancy

Refer to the core protocol (Section 8.3.13).

12.6.2.10.2 Medication Error

Refer to the core protocol (Section 8.3.14).

12.6.2.10.3 Overdose

Refer to the core protocol (Section 8.4).

12.6.3 Human Biological Samples

12.6.3.1 Pharmacokinetics

The PK of AZD0466 will be assessed when administered alone and in combination with voriconazole as described in the SoA (Table 25).

12.6.3.1.1 Blood Sample for Plasma Pharmacokinetics

Blood samples should be taken from a different part of the body than where study the treatment is being infused, including if central line access is available, to prevent erroneous drug concentration readings. For example, if AZD0466 is being infused into the patient's right arm, then the blood sample should be collected from the left arm.

Blood Samples for Plasma Pharmacokinetics

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)[a]
		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)[a]
	Day 8	Pre-infusion
		End of the infusion (+10 minutes)[a]
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)[a]
		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)[b]
	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)[a]
Cycle 3 and beyond	Day 1	Pre-infusion
		End of the infusion (+10 minutes)[a]

[a] As close as possible to the end of the infusion, but permissible up to 10 minutes.
[b] In the event that a planned collection is no longer possible at the scheduled timepoint, the Medical Monitor must be informed, and any collection outside allotted window must be discussed with the Medical Monitor.

12.6.3.2 Pharmacodynamics

12.6.3.2.1 CCI [redacted]

Mandatory whole blood samples will be collected from all patients at the timepoints indicated in the SoA (Table 25 and Table 26) and as shown below. CCI [redacted]

Note: Collection time begins with the start of infusion.

CCI

12.6.3.2.2 Blood for Pharmacodynamic CCI

Mandatory whole blood samples will be collected from all patients at the timepoints indicated in the SoA (Table 25 and Table 26) and as shown below. CCI

Blood for Pharmacodynamic CCI [redacted]

Study period	Day	Ramp-up (RU) or Target Dose (TD)	Timepoint
Screening	-	-	-
Cycle 1 Period 1	Day 1	RU1 Day 1	Pre-infusion
			End of infusion (+10 min)
			6 hours after start of infusion (± 30 min)
	Day 2	RU1 Day 2	24 hours after start of Day 1 infusion (± 2 hours)
	Day 4	RU2 Day 1	Pre-infusion
	Day 5	RU2 Day 2	24 hours after start of Day 4 infusion (± 2 hours)
	Day 8	TD Day 1	Pre-infusion
			End of infusion (+10 min)
			6 hours after start of infusion (± 30 min)
	Day 9	TD Day 2	24 hours after start of Day 8 infusion (± 2 hours)
Cycle 1 Period 3	Day 15	-	Pre-infusion
			End of infusion (+10 min)
			6 hours after start of infusion (± 30 min)
	Day 16	-	24 hours after start of Day 15 infusion (± 2 hours)
Cycle 2	Day 1	-	Pre-infusion
	Day 2	-	24 hours after start of Day 1 infusion (± 2 hours)
Disease Progression/ End of treatment	-	-	End of treatment

12.6.3.2.3 Peripheral Blood Smears

Mandatory peripheral blood smears will be collected at the timepoints indicated in the SoA (Table 25 and Table 26) and as shown below to evaluate CCI [redacted] normal blood cells and detect morphologic apoptotic responses in the blood. Blood smears will be obtained from collected CBC samples. Note: Collection time begins with the start of infusion.

Peripheral Blood Smears

Study period	Day	Ramp-up (RU) or Target Dose (TD)	Timepoint
Screening	-	-	-
Cycle 1 Period 1	Day 1	RU1 Day 1	Pre-infusion
			End of infusion (+10 min)
	Day 2	RU1 Day 2	24 hours after start of Day 1 infusion (± 2 hours)

	Day 4	RU2 Day 1	Pre-infusion
			End of infusion (+10 min)
	Day 5	RU2 Day 2	24 hours after start of Day 4 infusion (± 2 hours)
	Day 8	TD Day 1	Pre-infusion
			End of infusion (+10 min)
	Day 9	TD Day 2	24 hours after start of Day 8 infusion (± 2 hours)
Cycle 1 Period 3	Day 15	-	Pre-infusion
			End of infusion (+10 min)
			6 hours after start of infusion (± 30 min)
	Day 16	-	24 hours after start of Day 15 infusion (± 2 hours)
Cycle 2	Day 1	-	Pre-infusion
	Day 2	-	24 hours after start of Day 1 infusion (± 2 hours)
Disease Progression/ End of treatment	-	-	End of treatment

12.6.4 Human Biological Sample Biomarkers

12.6.4.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study, the patient consents to the mandatory research components of the study.

Samples for biomarker research are required and will be collected from all patients in this study as specified in the SoA (Table 25 and Table 26).

12.6.4.1.1 CCI

CCI [redacted]

CCI [redacted]

12.6.4.1.2 CCI

CCI

CCI

12.6.4.1.3 Bone Marrow Biopsy and Aspirate CCI

A mandatory pretreatment bone marrow biopsy and aspirate will be required for standard disease profiling CCI (Section 12.6.1). Bone marrow biopsy samples will be collected in accordance with local/institutional guidelines and as per the process delineated in the laboratory manual. CCI

Mandatory biomarker analysis will be also performed for any bone marrow biopsy and aspirate collected for disease assessment and at disease progression, according to the timepoints in Table 25 and Table 26.

Note: The disease progression sample may be taken at the safety follow-up visit if not collected previously.

12.7 Statistical Considerations – Module 2

12.7.1 Statistical Hypotheses

No formal statistical hypothesis testing is planned.

12.7.2 Sample Size Determination

The number of subjects is based on the desire to gain adequate information on the effect of voriconazole on the exposure of AZD4320, while exposing as few subjects as possible to study procedures.

Interpretation of the results will be based on the estimated effect (geometric mean ratio; GMR) and associated 90% CI.

Assuming an intrapatient CV of 30%, 10 PK evaluable participants are expected to give a relative precision of 2.0 (ratio between the upper and lower limits of the 90% CI) with a probability greater than 80%. This corresponds to a 90% CI of 2.83 to 5.66 if the observed ratio is 4.00 (based on in-vitro data). Up to 14 patients will be enrolled to ensure that at least 10 evaluable patients complete the study.

12.7.3 Populations for Analysis

The following populations for analyses are defined in Table 30.

Table 30 Populations for Analysis

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

12.7.4 Statistical Analyses

The SAP will include a more technical and detailed description of the statistical analyses described in this section.

12.7.5 General Considerations

Refer to the core protocol (Section 9.5) 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.

12.7.6 Efficacy

Refer to the core protocol (Section 9.6).

12.7.7 Safety

Refer to the core protocol (Section 9.7).

12.7.8 Other Analyses

12.7.8.1 Pharmacokinetics

Calculation or Derivation of Pharmacokinetic Variables

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

Plasma

C_{max}	Maximum observed plasma (peak) drug concentration
t_{max}	Time to reach peak or maximum observed concentration or response following drug administration
λz	Terminal rate constant, estimated by log-linear least squares regression of the terminal part of the concentration-time curve
$t_{1/2}$λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
AUC_{0-72}	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
AUC_{cml}	Area under the plasma concentration-curve from time 0 on Day 1 through the first full dose on Day 8 and extrapolated through infinity.
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:

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

Additional PK parameters may be calculated as appropriate.

PK Summary Statistics

Plasma concentrations of AZD4320 will be summarised by nominal sample time. Plasma concentrations and derived PK parameters will be summarised by dose level and cohort. Plasma concentrations at each timepoint will be summarised according to dose and cohort by

the following summary statistics:

- The geometric mean (g_{mean}, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (CV, calculated as 100 √ [exp(s2)-1], where s is the standard deviation of the data on a log scale)
- G_{mean} ± standard deviation (calculated as exp[μ±s])
- Arithmetic mean calculated using untransformed data
- Standard Deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for the estimated PK parameters, as appropriate:

- G_{mean}, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- CV, calculated as 100 √ [exp(s2)-1], where s is the standard deviation of the data on a log scale)
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

The pharmacokinetic data for AZD4320 will also be displayed graphically. Displays will include AZD4320 (total and released) plasma concentration subject profiles (on the linear and log scale) versus time and G_{mean} concentration (±standard deviation) versus time, stratified by dose.

Statistical Analysis of Pharmacokinetic Data

For the statistical analyses, only patients who provide eligible PK data for both AZD0466 (Period 1) and AZD0466 + Voriconazole (Period 3) interventions will be included for statistical comparison. A comparison of the AZD0466 PK parameters C_{max} and AUC will be performed for AZD0466 + Voriconazole versus AZD0466 interventions.

Where data allow, the statistical analysis will be performed via a linear mixed effect model using the natural logarithm of AZD4320 C_{max} and AUC as the response variables with

intervention as a fixed effect, and patient as a random effect. Transformed back from the logarithmic scale, geometric means together with CIs (2-sided 95%) for C_{max} and AUC will be estimated and presented. Also, ratios of geometric means together with CIs (2-sided 90%) will be estimated and presented.

12.7.9 Interim Analyses

No IA is planned.

12.8 References - Module 2

Voriconazole Prescribing Information
Highlights of Voriconazole Prescribing Information, VFEND (Revised 1/2019). Available from:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021630s034,021266s045,021267s055lbl.pdf. Accessed 28 October 2020.

13 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

None.

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

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

Regulatory Reporting Requirements for SAEs

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

  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure (or state other documents) and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

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

A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Patients or their legally authorised representative "an individual, juridical, or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial", per ICH GCP E6(R2) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorised representative.

A patient who is re-screened is not required to sign another ICF if the re-screening occurs within 28 days from the previous ICF signature date. A patient may be re-screened up to 2 times to determine eligibility in this study.

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

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorised designee will explain to each patient the objectives of the analysis to be done on the samples and any potential future use. Patients will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data Protection

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. In some cases, such wording will be in a separate accompanying document. AstraZeneca will not provide individual genotype results to patients, their family members, their general physician, any insurance company, any employer, or any other third party, unless required to do so by law; however, AstraZeneca may share data and biosamples with research partners.

Precautions are taken to preserve confidentiality and prevent genetic data from being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and might also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files. Even so, the patient's medical information and the genetic files would remain physically separate.

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information that would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the patient in the informed consent.

- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

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

The SRC will consist of:

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

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

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

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

Further internal or external experts may be consulted by the SRC as necessary. The Global Safety Physician or delegate should always be present at the SRC if there are safety issues for discussion.

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

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

A 8 Source Documents

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

- All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the construction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).
- A digital copy of all imaging scans should be stored as source documents.

A 9 Study and Site Start and Closure

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

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

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

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

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

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

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

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

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the sponsor

before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a co-ordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (ICMJE) authorship requirements.

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

B 1 Definition of Adverse Events

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

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

B 2 Definition of Serious Adverse Events

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

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

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

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

Life-threatening

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

Hospitalisation

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

Important Medical Event or Medical Treatment

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

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

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

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

The grading scales found in the revised National Cancer Institute CTCAE version 5 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

B 3 A Guide to Interpreting the Causality Question

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

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

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

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

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

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

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

B 4 Medication Error

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

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

Medication error includes situations where an error:

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

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

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, eg, wrong route or wrong site of administration

- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding IRT errors)
- Wrong drug administered to patient (excluding IRT errors)

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

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

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

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

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

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

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

The Investigator:

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

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

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

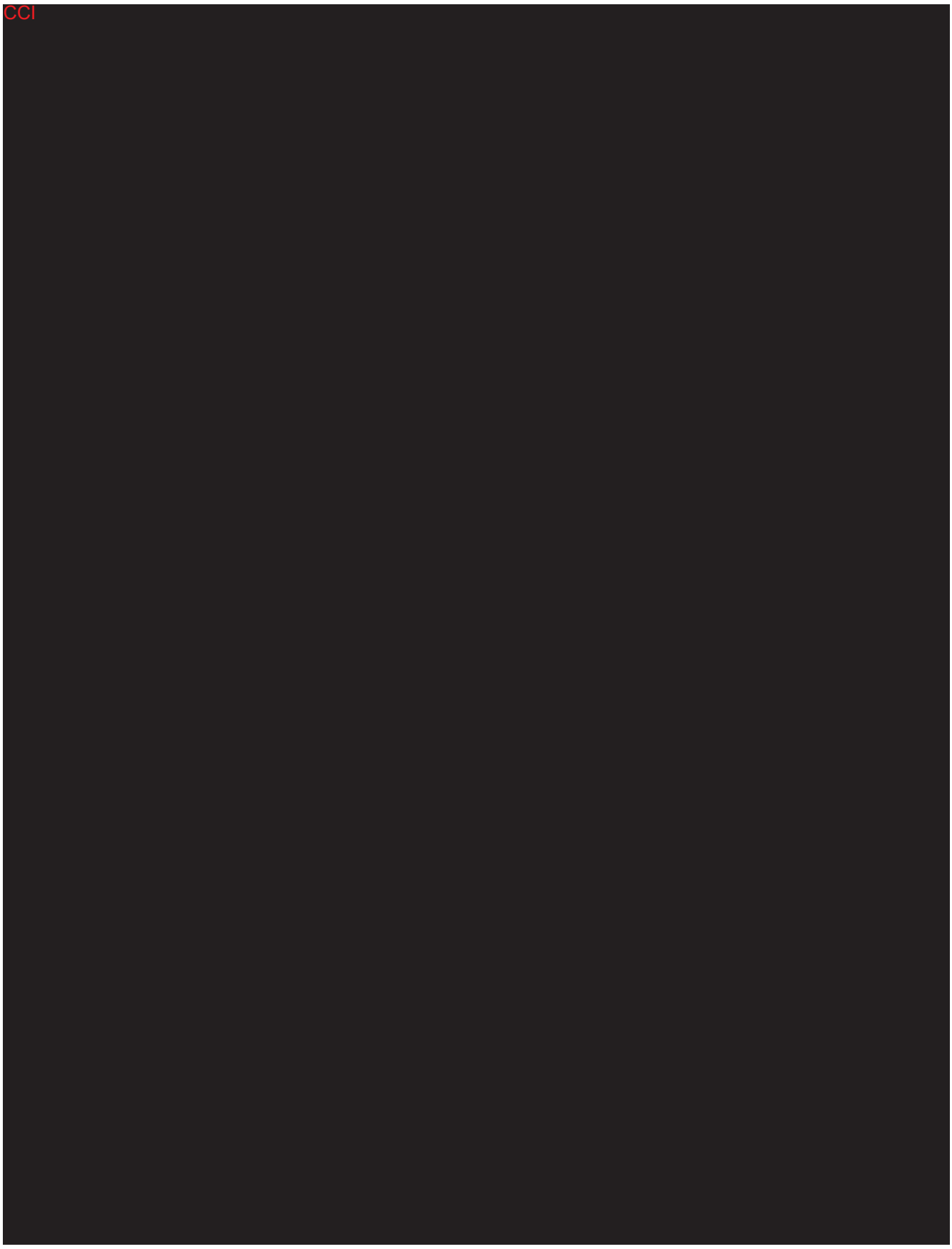
- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf)
- Biological samples transported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

Appendix D Optional Genomics Initiative Sample

D 1 CCI

CCI

CCI

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

E 1 Introduction

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

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

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

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

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

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

E 2 Definitions

Potential Hy's Law
Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3× Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

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

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

E 3 Identification of Potential Hy's Law Cases

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

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

Local Laboratories Being Used:

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

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

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

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

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

E 4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (see Section E 6)
- Notify the AstraZeneca representative who will then inform the central Study Team

- Within one day of PHL criteria being met, the Investigator will report the case as a SAE of Potential HL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting
- For patients that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the patient's condition
- The Medical Monitor contacts the Investigator, to provide guidance, discuss and agree an approach for patient follow-up (including any further laboratory testing), and the continuous review of data
- Subsequent to this contact the Investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Medical Monitor
  - Complete the 3 Liver eCRF Modules as information becomes available

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

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

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

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

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential HL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

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

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

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

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

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

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

At the first on-study treatment occurrence of PHL criteria being met the Investigator will determine if there has been a **significant change** in the patients' condition[#] compared with the last visit where PHL criteria were met**:**

- If there is no significant change no action is required
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section E 4.2.

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

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

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

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

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

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

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

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

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

E 8 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests, which are recommended but not mandatory. The list may be modified based on clinical judgement. Any test results need to be recorded.

Hy's Law Lab Kit for Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA[a] IgG anti-HCV HCV RNA[b] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate-deficient transferrin (CD-transferrin)
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive

E 9 References

Aithal et al, 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H,et al Case definition and phenotype standardization in drug-induced liver injury. Clinical Pharmacology and

Therapeutics. 2011; 89(6):806-15.

FDA Guidance for Industry, July 2009

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

Appendix F Management of Specific Adverse Events

F 1 Guidance for Management of Tumour Lysis Syndrome

Patients will be evaluated for clinical signs and symptoms of TLS during treatment with AZD0466, and blood samples will be collected according to the individual module SoA.

Recommendations for prophylaxis, management, dose modification, and adverse event reporting pertaining to TLS are summarised below.

F 1.1 Prophylaxis for TLS

Assessment of TLS risk is based on disease type, as summarised in Table 31.

Table 31 Risk Assessment for Tumour Lysis Syndrome

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

[a] WBC < 10 ×10^9/L is required for study eligibility and hydroxyurea (AML) and high-dose steroids (ALL and leukaemia of ambiguous lineage) are 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.
LDH, lactate dehydrogenase; TLS, tumour lysis syndrome; ULN, upper limit of normal range; WBC, white blood cell count.

Prophylaxis for TLS (hydration and anti-hyperuricaemic agents) is required for all patients receiving study treatment and should be implemented according to the TLS risk level assessed for each patient (Table 31). Specific recommendations are outlined in this section, but details of management may vary per institutional practice. Patients with creatinine clearance < 80 mL/min, and patients with renal involvement from underlying disease and/or urinary outflow obstruction, may be at higher risk of TLS and complications of TLS, and should be managed accordingly. Hospitalisation may be considered for hydration management requirements occurring outside of the protocol-scheduled inpatient hospitalisation period.

Prophylaxis is summarised by TLS risk score in Table 32, according to the following principles:

- **Adequate oral fluid intake** (Table 32) is required for all patients receiving study treatment, in particular around the times of AZD0466 dosing, and patients should be

encouraged to drink sufficient fluid (total of 1.5 to 2 L/day) before and after each infusion of AZD0466.

- **IV hydration** is required for all patients during the ramp-up in Cycle 1 (total > 2 L/day of IV and oral hydration). From Cycle 1 Day 15 onwards, IV hydration should be administered based on risk of TLS. Infusion of sodium chloride 0.9% IV (fluid composition may change based on patient need and Investigator discretion) should commence 2 to 4 hours before each infusion of AZD0466. At least 1 L of IV hydration should be administered over a 24-hour period. Additional IV hydration may be administered as clinically indicated in patients with diarrhoea and/or nausea and vomiting. Diuretics should be used with care and prophylactic use of diuretics should be used only if patients have signs of volume overload.
- **Allopurinol** (or other xanthine oxidase inhibitor) should be administered to all patients receiving study treatment and it is recommended to initiate it one calendar day before the first dose of AZD0466. 100 to 300 mg every 8 hours is suggested, but allopurinol dose may require adjustment as described in the allopurinol prescribing information or institutional guidelines.
- **Rasburicase** should be considered as an alternative to allopurinol for patients with elevated uric acid at baseline, or high tumour burden. Rasburicase should be administered 4 hours prior to AZD0466 infusion, and as described in the rasburicase prescribing information. It is recommended that investigators check for Glucose-6-Phosphate-Dehydrogenase (G6PD) as Rasburicase is contraindicated in patients with G6PD deficiency.

Table 32 Recommended Prophylaxis for Tumour Lysis Syndrome

	Risk of tumour lysis syndrome		
	High	**Intermediate**	**Low**
Recommended prophylaxis			
Hydration	Increased hydration: oral 1.5 to 2 L/day and IV 150 to 200 mL/h Maintain urine output	IV hydration required during ramp-up (total IV and oral fluids > 2 L/day) From Cycle 1 Day 15: oral hydration 1.5 to 2 L/day; consider IV hydration based on risk of TLS	
Anti-hyperuricaemics	Allopurinol 100 to 300 mg every 8 hours Early consideration of rasburicase[a] as an alternative, based on baseline uric acid and tumour burden		Allopurinol 100 to 300 mg every 8 hours
Criteria for use of rasburicase			
Serum uric acid at baseline	> 475.8 µmol/L[b] + 1 risk factor ≤ 475.8 µmol/L[b] + 2 risk factors	> 475.8 µmol/L[b] + 2 risk factors ≤ 475.8 µmol/L[b] + 3 risk factors	-
Risk factors	Serum creatinine > 1.3 mg/dL (> 88.4 µmol/L) WBC > 50 $\times 10^9$/L LDH > 2x ULN		-

[a] Rasburicase is contraindicated in patients with glucose-6 phosphate dehydrogenase deficiency, known hypersensitivity to rasburicase, haemolytic anaemia or methemoglobinemia
[b] Uric acid cut-off may be adjusted according to local guidance.
Recommended prophylaxis adapted from University of Texas MD Anderson Cancer Center 2018, Cairo and Bishop 2004,Cairo and Bishop 2004
Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127(1):3-11.

, and Howard et al 2011.
IV, intravenous; LDH, lactate dehydrogenase; ULN, upper limit of normal range; TLS, tumour lysis syndrome; WBC, white blood cell count.

F 1.2 AZD0466 Dose Modifications for TLS

AZD0466 dose modifications for TLS are summarised in Table 33.

Table 33 AZD0466 Dose Modifications for TLS

Abnormality	Action with AZD0466
Laboratory findings (serum)	
Uric acid ≥ 475.8 µmol/L	• Initiate supportive therapy as per standard clinical practice, additional guidance provided in Table 34. • Delay AZD0466 for up to 7 days (if finding present before administration of AZD0466) • If resolution to within specified threshold in ≤ 7 days, restart AZD0466 at the **same dose level** • If resolution after 7 days, restart AZD0466 at **one lower dose** than the current dose.
Potassium ≥ 6.0 mmol/L	
Phosphate ≥ 1.6 mmol/L (5.0 mg/dL) with ≥ 0.16 mmol/L (0.5 mg/dL) increase*	
Corrected calcium < 1.75 mmol/L	
Creatinine increase by > 26.5 µmol/L from baseline (creatinine > 1.5 x ULN if no baseline)	
All laboratory abnormalities must resolve to within specified threshold before AZD0466 is restarted, with the exception of an isolated phosphate abnormality, in which instance restarting the dose may be discussed with the Medical Monitor.	
Clinical findings	
Signs suggestive of clinical TLS (eg, acute kidney injury, cardiac arrhythmia/dysrhythmia[a], hypotension[b], heart failure[b])	• Initiate supportive therapy as per standard clinical practice • Delay AZD0466 for up to 14 days (if finding present before administration of AZD0466) • Restart AZD0466 at **one lower dose** than the current dose following resolution
Symptoms suggestive of clinical TLS[a] (eg, oliguria[c], seizure, nausea, vomiting, muscle cramps[b], neuromuscular instability[b])	• For clinical TLS, initiate supportive therapy and withhold AZD0466 until resolution of symptoms. AZD0466 can be withheld up to 14 days. • Restart AZD0466 at **one lower dose** than the current dose level • Patients should be encouraged to maintain oral hydration

[a] Probably or definitely caused by hyperkalaemia or hypocalcaemia
[b] Probably or definitely caused by hypocalcaemia
[c] Average urine output of < 0.5 mL/kg/h, lasting for > 6 hours.
TLS, tumour lysis syndrome; ULN, upper limit of normal range.
*Recommended prophylaxis adapted from University of Texas MD Anderson Cancer Center 2018, Cairo and Bishop 2004, Coiffier et al 2008, and Howard et al 2011.
.

F 1.3 Treatment of TLS

Signs and symptoms of clinical TLS (including but not limited to acute kidney injury, oliguria, nausea, vomiting, seizure, muscle cramps, neuromuscular irritability, cardiac arrhythmia/dysrhythmia, hypotension, or heart failure) should be managed according to standard clinical practice. Additional IV hydration may be administered as clinically indicated in patients with diarrhoea and/or nausea and vomiting.

Recommendations for management of specific laboratory abnormalities is summarised in Table 34.

Table 34 Recommended Management of Electrolyte Abnormalities in TLS

Abnormality	Management recommendations
Hyperphosphataemia	
Moderate (≥ 2.1 mmol/L)	Avoid IV and oral phosphate and limit dietary sources Administer phosphate binder
Severe	Dialysis or haemofiltration may be required
Hypocalcaemia (≤ 1.75 mmol/L)	
Asymptomatic	No therapy Patients with acute hypocalcaemia and hyperphosphataemia should not receive calcium repletion until phosphate level has normalised
Symptomatic	Calcium gluconate[a] 50 to 100 mg/kg by slow IV infusion with ECG monitoring
Calcium-phosphate product	
≥ 50 mg^2/dL^2	Ensure hydration is maintained and alkalinisation is discontinued
Hyperkalaemia	
Moderate (≥ 6.0 to < 7.0 mmol/L) and asymptomatic	Avoid IV and oral potassium ECG monitoring Administer sodium polystyrene sulfonate
Severe (≥ 7.0 mmol/L) or symptomatic	As above, plus Calcium gluconate[a] 100 to 200 mg/kg by slow IV infusion if concurrent ECG changes (including life-threatening arrhythmias) Regular IV insulin and dextrose, monitor blood glucose closely Consider sodium bicarbonate[a] if patient is acidaemic Consider albuterol (to be avoided in patients with acute coronary disease) Dialysis may be required
Renal dysfunction (uraemia)	Fluid and electrolyte management Uric acid and phosphate management Adjust doses of renally excreted medication Dialysis or haemofiltration may be required

[a] Sodium bicarbonate and calcium gluconate should not be administered through the same line.
Recommended management adapted from University of Texas MD Anderson Cancer Center 2018, and Coiffier et al 2008. ECG, electrocardiogram; IV, intravenous.

Laboratory parameters indicating TLS (including blood urea nitrogen, creatinine, phosphate/phosphorus, uric acid, calcium, potassium, and lactate dehydrogenase [LDH]) will be evaluated. Fluid balance must be monitored per institutional standards. If more aggressive hydration management is indicated, patient hospitalisation will be considered at Investigator discretion. Allopurinol prophylaxis should be considered based on institutional guidelines.

F 1.4 Reporting Adverse Events of TLS

The Investigator will report TLS as an adverse event or serious adverse event of "laboratory

TLS" or "clinical TLS" according to the classification of TLS in Appendix G 1. For the purposes of adverse event reporting, a CTCAE grade for TLS should also be recorded, as follows:

- CTCAE Grade 3: TLS present
- CTCAE Grade 4: TLS with life-threatening consequences; urgent intervention indicated
- CTCAE Grade 5: Death

TLS will also be graded according to Cairo-Bishop criteria for the purposes of dose-limiting toxicity assessment and summary of adverse events of special interest (Appendix G 2; Cairo and Bishop 2004).

F 2 Guidance for Management of haematological changes

F 2.1 Thrombocytopenia and Haemorrhage

Platelet transfusions are permitted as per institutional standards. However, due to the mechanism of action of AZD0466, platelet transfusion may have limited efficacy within 24 to 48 hours after AZD0466 infusion.

AZD0466 should be withheld in presence of significant bleeding events with or without thrombocytopenia, such as:

- Grade 3 or 4 haemorrhage
- Any grade serious haemorrhage event
- Any grade intracranial haemorrhage or haematoma

However, if there is evidence that the patient is experiencing clinical benefit with AZD0466, restarting at a reduced dose may be considered following discussion with the Medical Monitor. AZD0466 should be discontinued if significant bleeding reoccurs.

Anticoagulants and aspirin are not allowed during the study; other anti-aggregants may be used with caution.

F 2.2 Neutropenia and Febrile Neutropenia

The use of G-CSF (eg, filgrastim) or GM-CSF (eg, sargramostim) may be used for management of severe neutropenia or febrile neutropenia, according to institutional standards provided the patient has < 5% blasts in bone marrow and it is discussed with the Medical Monitor. The use of long-acting pegylated G-CSF (eg, pegfilgrastim) is not permitted during study treatment.

G-CSF or GM-CSF should not be administered within 72 hours prior to performing bone

marrow assessments.

F 2.3 Leucocyte Count

With the exception of hydroxyurea (AML) and high-dose steroids (ALL and leukaemia of ambiguous lineage) during screening and Cycle 1 up to 4 days (maximum dexamethasone IV 40 mg/day or equivalent), no other direct anti-leukaemia therapy is permitted once study treatment has begun. Both medications are to be used for white blood cell count control and can be started or stopped any point during this period.

F 2.4 Anaemia

Patients already receiving erythropoietin at screening may continue to receive it during study treatment, provided they have been receiving erythropoietin for > 1 month at the time study treatment is started.

Prophylaxis in Cycle 1: Prophylactic erythropoietin should not be started during Cycle 1.

Prophylaxis in cycle 2 and beyond: Prophylactic erythropoietin may be started during Cycle 2 or in subsequent cycles.

Use of the long-acting erythropoiesis-stimulating agent, darbepoetin, is not permitted during study treatment.

Blood transfusions may be administered at the discretion of the Investigator.

F 3 Guidance for Management of Fungal Infection

In vitro data have shown that the principal CYP enzyme responsible for the Phase I metabolism of AZD0466 is CYP3A4. Azole antifungal agents including ketoconazole, itraconazole, voriconazole, posaconazole, and fluconazole are strong or moderate inhibitors of CYP3A4. As there is no data available at the time of initiation of this protocol on in vivo interactions between azole antifungal agents and AZD0466, use of this class of agents is prohibited during study treatment (with the exception of per protocol administration of voriconazole in Module 2).

Therapeutic: Non-azole antifungal agents (eg, caspofungin) should be given in the first instance. However, should an azole antifungal be necessary, it may be administered a minimum of 24 hours after the last dose of AZD0466 and AZD0466 should be discontinued. If there is evidence that the patient is experiencing clinical benefit with AZD0466, restarting at a reduced dose may be considered following discussion with the Medical Monitor.

Prophylactic: Non-azole antifungal agents (eg, caspofungin) should be considered for patients at risk of prolonged neutropenia (> 10 days) to reduce the risk of fungal infections.

The potential drug-drug interaction between AZD0466 and an azole antifungal agent will be investigated in Module 2 of this protocol. Guidance on concomitant use of azole antifungal agents will be updated by protocol amendment, if applicable based on emerging data.

F 4 References

Cairo and Bishop 2004
Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127(1):3-11.

Coiffier et al 2008
Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008; 26(16):2767-78.

Howard et al 2011
Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med 2011;364(19):1844-54.

University of Texas MD Anderson Cancer Center 2018
Tumor lysis syndrome (TLS) in adult patients 2018. Copyright University of Texas MD Anderson Cancer Center 2018.

Appendix G Classification of Tumour Lysis Syndrome

G 1 Classification

The criteria for classification of laboratory and clinical TLS in adults are described below. These criteria are based on the Howard et al 2011 modification of Cairo and Bishop 2004, and have been adapted from Cheson et al 2017.

Clinical TLS assumes the laboratory evidence of metabolic changes and an adverse event that requires clinical intervention. Clinical TLS is defined as the presence of laboratory TLS and any one or more of the clinical criteria, as specified in Table 35 below.

Table 35 Criteria for Laboratory and Clinical Tumour Lysis Syndrome

Abnormality	Criteria
Laboratory TLS	
Two or more of the following metabolic abnormalities occurring during the same 24-hour period, and within 3 days before until 7 days after infusion of study treatment:	
Hyperuricaemia	Uric acid ≥ 475.8 µmol/L (≥ 8.0 mg/dL)
Hyperkalaemia	Potassium ≥ 6.0 mmol/L
Hyperphosphataemia	Phosphate ≥ 1.5 mmol/L (≥ 4.5 mg/dL)
Hypocalcaemia	Corrected calcium < 1.75 mmol/L (< 7.0 mg/dL), or Ionised calcium < 0.3 mmol/L
Clinical TLS	
Laboratory TLS plus one or more of the following:	
Acute kidney injury	Serum creatinine increase by > 26.5 µmol/L (or a single value > 1.5 × ULN if no baseline measurement), or oliguria (average urine output of < 0.5 mL/kg/h) lasting for > 6 hours
Cardiac arrhythmia/dysrhythmia or sudden death	Probably or definitely caused by hyperkalaemia or hypocalcaemia
Seizure	Probably or definitely caused by hypocalcaemia
Neuromuscular irritability, hypotension, or heart failure	Probably or definitely caused by hypocalcaemia

TLS, tumour lysis syndrome; ULN, upper limit of normal.

G 2 Grading

TLS should be graded according to the Cairo-Bishop criteria for the purposes of dose-limiting toxicity assessment (Cairo and Bishop 2004). The grade of the maximal clinical manifestation defines the overall grade of TLS, as summarised below in Table 36.

Table 36 Grading of Tumour Lysis Syndrome

Cairo-Bishop Grading for TLS						
Abnormality	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Laboratory TLS	Absent	Present	Present	Present	Present	Present
Serum creatinine[a]	< 1.5 x ULN	1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN	Death[b]
Cardiac arrhythmia[a]	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (eg, defibrillator)	Life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	Death[b]
Seizure[a]	None	--	One brief generalised seizure; seizures well controlled by anticonvulsants; infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalised seizures despite medical intervention	Seizure of any kind and prolonged, repetitive or difficult to control (eg, status epilepticus, intractable epilepsy)	Death[b]

[a] Not directly or probably attributable to a concomitant therapeutic agent.
[b] Probably or definitely attributable to clinical TLS.
Modified from Cairo and Bishop 2004.
ADL, activities of daily living; CHF, congestive heart failure; TLS, tumour lysis syndrome; ULN, upper limit of normal.

G 3 References

Cairo and Bishop 2004
Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127(1):3-11

Cheson et al 2017
Cheson BD, Enschede SH, Cerri E, Desai M, Potluri J, Lamanna N et al. Tumor lysis syndrome in chronic lymphocytic leukemia with novel targeted agents. Oncologist. 2017;22(11):1283-91.

Howard et al 2011
Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med 2011;364(19):1844-54.

Appendix H Drugs That Prolong QT Interval and/or Induce Torsades De Pointes

Drugs with known or possible risk of TdP (cardiac arrhythmia due to drug-induced QTc prolongation) are withheld for 5 half-lives prior to the first dose of study treatment and will continue to be withheld during the study, and for 14 days after the last dose of AZD0466.

Table 37 Drugs with a known risk of Torsades de Pointes

Contraindicated drug	Withdrawal period prior to the start of study treatment
Aclarubicin, anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine, terlipressin.	2 days
Cilostazol, cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, sotalol, roxithromycin, sevoflurane, sparfloxacin, thioridazine	7 days
Azithromycin, bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine, citalopram, dronedarone, escitalopram, fluconazole, levomepromazine, levosulpiride	14 days
Donepezil, terodiline	3 weeks
Levomethadyl, methadone, pimozide	3 weeks[b]
Arsenic trioxidea, ibogaine	3 weeks[b]
Pentamidine	3 weeks[b]
Astemizole, probucol, vandetanib	3 weeks[b]
Amiodarone, chloroquine	1 year

[a] Estimated value, as pharmacokinetics of arsenic trioxide have not been studied.
[b] The withdrawal period for these drugs will be 3 weeks prior to the start of study treatment, after discussion with the Medical Monitor regarding the risk/benefit ratio.

CredibleMeds® (www.crediblemeds.org) is the standard reference for drugs with known or possible risk of TdP. Since CredibleMeds® constantly assesses new drug information and updates its lists, sites should go directly to the crediblemeds.org website in real-time for reference. Patients receiving drugs listed in the “known” or “possible” categories at the time of eligibility assessment are prohibited from 14 days before the start of treatment until permanent discontinuation of treatment.

Some of the medications listed as a possible risk of TdP may be allowed at the Investigator's discretion after approval by the Medical Monitor when the patient has unmet medical need to continue receiving prohibited medication(s), no suitable alternative treatments are available, and the benefit-risk ratio is acceptable in the Investigator's opinion.

Appendix I Contraception Guidance

I 1 Definitions

- A female of childbearing potential is defined as a female who is not permanently surgically sterilised or postmenopausal.
- Surgical sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion (the term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).
- Postmenopausal is defined as amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:
  - Women under 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments AND with luteinising hormone and follicle-stimulating hormone levels in the postmenopausal range
  - Women over 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments
- A highly effective method of contraception is defined as a method that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly.

I 2 Contraception Methods

Highly effective methods of contraception are described in Table 38.

Table 38 Highly Effective Methods of Contraception

Barrier/Intrauterine Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomised partner [a] • Sexual abstinence [b]	Combined (oestrogen and progestogen containing [c] hormonal contraception) ° Oral (combined pill) ° Injectable ° Transdermal (patch) Progestogen-only hormonal contraception associated with inhibition of ovulation [d] ° Injectable ° Implantable

[a] With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).

[b] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the subject. However, periodic or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

[c] Hormonal contraception may be susceptible to interaction with study or other drugs, which may reduce the efficacy of the contraception method. Women using hormonal contraceptives must add a barrier method.

[d] Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (eg, minipill), is not accepted as a highly effective method.

Appendix J Response Evaluation Criteria for Acute Myeloid Leukaemia

These criteria are based on the Döhner et al 2017 revised recommendations of the international working group for diagnosis, standardisation of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukaemia (Döhner et al 2017).

Category	Definition
Response	
CR without minimal residual disease (CR_{MRD-})	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC
Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 × 10^9/L (1000/µL); platelet count ≥100 × 10^9/L (100 000/µL)
CR with incomplete haematologic recovery (CR_i)	All CR criteria except for residual neutropenia (<1.0 × 10^9/L [1000/µL]) or thrombocytopenia (<100 × 10^9/L [100 000/µL])
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no haematologic recovery required
Partial remission (PR)	All haematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Treatment failure	
Primary refractory disease	No CR or CR_i after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause
Death in aplasia	Deaths occurring ≥7 d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 d of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 d following its completion; or deaths occurring ≥7 d following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Response criteria for clinical trials only	
Stable disease	Absence of CR_{MRD-}, CR, CR_i, PR, MLFS; and criteria for PD not met
Progressive disease (PD) [a] [b]	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level (>0.5 × 10^9/L [500/µL], and/or platelet count to >50 × 10^9/L [50 000/µL] nontransfused); or • >50% increase in peripheral blasts (WBC × % blasts) to >25 × 10^9/L (>25 000/µL) (in the absence of differentiation syndrome) [b]; or • New extramedullary disease
Relapse	

Category	Definition
Haematologic relapse (after CR_{MRD-}, CR, CR_i)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease
Molecular relapse (after CR_{MRD-})	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by MFC

[a] The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonising the various definitions used in different clinical trials.

[b] Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.

ANC, absolute neutrophil count; d, day; IDH, isocitrate dehydrogenase; MFC, multiparameter flow cytometry; mo, month; RT-qPCR, real-time quantitative polymerase chain reaction; WBC, white blood cell.

J 1 References

Döhner et al 2017

Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-47.

Appendix K Response Assessment for Acute Lymphoblastic Leukaemia

Disease Status Criteria for acute lymphoblastic leukaemia (ALL):

At least 20% lymphoblasts present in blood or marrow at baseline. Immunophenotyping must be performed to determine lineage (B-cell, T-cell, or mixed B/T-cell).

Extramedullary Disease in ALL:

1 Measurable Extramedullary Disease: Lesions that can be accurately measured in 2 dimensions by CT or MRI.

2 Non-measurable Extramedullary Disease: All other lesions including unidimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusion, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed or followed by imaging techniques or disease documented by indirect evidence only (eg, lab values).

For patients with extramedullary disease, baseline disease assessments will be performed using radiologic imaging by CT with contrast covering neck, chest, abdomen, and pelvis within 30 days before the first dose of study treatment. Radiologic scans (ie, contrast CT) will be repeated approximately every 12 weeks ±7 days. Up to 6 measurable extramedullary disease lesions (only target lesions >1.0 cm in the longest diameter may be assessed), clearly measurable in 2 perpendicular dimensions, will be followed as target lesions for each patient. Measurable sites of disease should be chosen such that they are representative of the patient's disease. In addition, selection of target lesions should be from as disparate regions of the body as possible when these areas are significantly involved. If additional non-measurable extramedullary disease lesions are present, they can be added as non-target lesions and followed throughout the study. For patients with baseline hepatosplenomegaly, the cranial-caudal measurement of the spleen and longest diameter of the liver will be assessed at screening and all subsequent response evaluations. MRI may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable. In cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations.

Patients without extramedullary disease will be assessed for response every 4 weeks (±7 days)

Response Assessment (Advani et al 2022

Advani AS, Moseley A, O'Dwyer KM, Wood BL, Fang M, Wieduwilt MJ, et al. SWOG 1318: A Phase II Trial of Blinatumomab Followed by POMP Maintenance in Older Patients With Newly Diagnosed Philadelphia Chromosome-Negative B-Cell Acute Lymphoblastic Leukemia. J Clin Oncol 2022; 40(14):1574-82

SWOG 2020; Advani et al 2022):

C1 extramedullary disease status: Complete disappearance of all measurable and non-

measurable extramedullary disease with the exception of lesions for which the following must be true: for patients with ≥ 1 measurable lesion, all nodal masses > 1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤ 1.5 cm in GTD and all nodal masses ≥ 1 cm and ≤ 1.5 cm in GTD at baseline must have regressed to < 1 cm GTD or they must have reduced by 75% in sum of products of greatest diameters (SPD). No new lesions. Spleen and other previously enlarged organs must have regressed in size and must not be palpable. All disease must be assessed using the same technique as at baseline.

C2 extramedullary disease status: Patient does not qualify for C1 status.

Complete Remission (CR)

1 < 5% marrow aspirate blasts. Blasts can be ≥ 5% if the blasts are found to be myeloid and there is no evidence of lymphoblasts by flow cytometry or immunostaining.
2 ANC ≥ 1,000 cells/mm3; platelets > 100,000 cells/mm3; and no blasts in the peripheral blood.
3 C1 extramedullary disease status as described above.

Complete Remission with Incomplete Recovery (CR_i)

Same as CR but platelet count may be ≤ 100,000 cells/mm^3 and/or ANC ≤ 1,000 cells/mm^3

Partial Remission (PR)

Improvement or no worsening of ALL, as indicated by all of the following:

1 No blasts in the peripheral blood
2 ANC ≥ 1,000 cells/mm^3; platelets > 100,000 cells/mm^3
3 Either or both of the following:
   – At least a 50% decrease in the marrow blast percentage, compared to the pretreatment value, and marrow blast percentage ≥ 5% and ≤ 25%.
   – C2 extramedullary disease status as described above.

FAILURE - Resistant Disease (RD)

Resistant Disease: Patient survives ≥ 7 days following completion of initial treatment course with persistent leukaemia in the last peripheral blood smear or bone marrow, or with persistent extramedullary disease.

FAILURE - Aplasia

Aplasia: Patient survives ≥ 7 days following completion of initial treatment course then dies while cytopenic, with the last post induction bone marrow aplastic or hypoplastic (ie, < 20% cellularity) and without leukaemia blasts.

FAILURE - Indeterminate

Indeterminate:

(a) Patient survives < 7 days after completion of initial treatment course; or

(b) patient survives ≥ 7 days following completion of initial treatment course then dies with no persistent leukaemia in the peripheral smear but no post-induction bone marrow examination.

RELAPSE FROM CR or CRi

Relapse: Reappearance of leukaemia blasts in the peripheral blood; or > 5% blasts in the bone marrow not attributable to another cause (eg, recovery of normal cells following chemotherapy-induced aplasia); or appearance or reappearance of extramedullary disease.

K 1 References

Advani et al 2022
Advani AS, Moseley A, O'Dwyer KM, Wood BL, Fang M, Wieduwilt MJ, et al. SWOG 1318: A Phase II Trial of Blinatumomab Followed by POMP Maintenance in Older Patients With Newly Diagnosed Philadelphia Chromosome-Negative B-Cell Acute Lymphoblastic Leukemia. J Clin Oncol 2022; 40(14):1574-82

SWOG 2020
SWOG Data Operations Center. Oncology Research Professional (ORP) Manual. Version 6.0 October 2020.
https://crawb.crab.org/txwb/CRA_MANUAL/Vol1/chapter%2011a_Response%20Assessment-Leukemia.pdf (Accessed 8 Dec 2020).

Appendix L Eastern Cooperative Oncology Group Performance Status Scoring

Eastern Cooperative Oncology Group (ECOG) performance status is scored as follows:

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

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

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

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

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

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

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study patients become infected with COVID-19 or similar pandemic infection) during which patients may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

M 1 Re-screening of Participants to Reconfirm Study Eligibility

Up to 2 additional re-screenings per patient can be performed for screen failures due to study disruption in previously screened patients. The Investigator should confirm this with the designated Medical Monitor.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment into the study or commencing of dosing with study treatment. If this delay is outside the screening window specified in the individual module SoA, the patient will need to be re-screened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a patient in addition to that detailed in Section 5. The procedures detailed in Section 5 must be undertaken to confirm eligibility using the same patient number for the same patient.

Appendix N New York Heart Association Functional Classification

Class	Patient Symptoms	Class	Objective Assessment
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath).	A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath).	B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.	C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.	D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Reference: https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure
Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.

Appendix O Prognostic Scoring for Myelodysplastic Syndrome

O 1 Prognostic Scoring System for MDS: The International Prognostic Scoring System – Revised (IPSS-R)

IPSS-R prognostic score values							
Prognostic variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**	**3.0**	**4.0**
% Bone Marrow blasts	≤ 2	-	> 2–< 5	-	5–10	> 10	-
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very Poor
Hemoglobin (g/dL)	≥ 10	-	8–< 10	< 8	-	-	-
Platelets ($\times 10^9$/L)	≥ 100	50–< 100	< 50	-	-	-	-
Neutrophils ($\times 10^9$/L)	≥ 0.8	< 0.8	-	-	-	-	-

IPSS-R prognostic risk categories	IPSS-R risk score
Very low	≤ 1.5
Low	> 1.5–3
Intermediate	> 3– 4.5
High	> 4.5–6
Very high	> 6

O 2 MDS Cytogenetic Scoring System

MDS cytogenetic prognostic subgroups	Cytogenetic abnormalities
Very good	−Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	−7, inv(3)/t(3q)/del(3q), double including −7/del(7q), complex: 3 abnormalities
Very poor	Complex: > 3 abnormalities

O 3 References

Greenberg et al 2012
Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012;120(12):2454-65.

Appendix P Response Criteria for Myelodysplastic Syndrome

P 1 Response Criteria (IWG 2006)

Category (IWG2006)	**Response Criteria (response must last at least 4 weeks)**
Complete remission	Bone marrow: • ≤ 5% myeloblasts with normal maturation of all cell lines [a] Persistent dysplasia will be noted[a,b]
	Peripheral blood [c]: • Hgb ≥ 11 g/dL • Platelets ≥ 100×10^9/L • Neutrophils ≥ 1.0×10^9/L[b] • Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except: • Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR [b]	Bone marrow CR: • ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment [b] Peripheral blood: • if HI responses, they will be noted in addition to marrow CR [b]
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: • Return to pretreatment bone marrow blast percentage • Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets • Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete cytogenetic response: • Disappearance of the chromosomal abnormality without appearance of new ones
	Partial cytogenetic response: • At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: • Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts • 5%-10% blasts: ≥ 50% increase to > 10% blasts • 10%-20% blasts: ≥ 50% increase to > 20% blasts • 20%-30% blasts: ≥ 50% increase to > 30% blasts
	Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets

Category (IWG2006)	Response Criteria (response must last at least 4 weeks)
	• Reduction in Hgb by ≥ 2 g/dL • Transfusion dependence

[a] Dysplastic changes should consider the normal range of dysplastic changes (modification).
[b] Modification to IWG response criteria.
[c] In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

AML, acute myeloid leukaemia; CR, complete remission; DFS, disease-free survival; FAB, French-American-British; Hgb, haemoglobin; HI, haematologic improvement; MDS, myelodysplastic syndromes; PR, partial remission; PFS, progression-free survival.

P 2 Haematological Improvement (IWG 2018)

Response evaluation criteria: Haematological Improvement - Erythrocytes, Platelets, and Neutrophils

Haematological improvement (IWG 2018)	Response criteria (response must last at least 8 weeks)
Baseline criteria	
Definition of transfusion-burden categories	3 groups: • NTD (0 RBCs in 16 weeks)[a] • LTB (3-7 RBCs in 16 weeks in at least 2 transfusion episodes, maximum 3 in 8 weeks) [a] • HTB (≥8 RBCs in 16 weeks, ≥4 in 8 weeks)
Pretreatment RBC transfusion policy	Transfusion policy for the individual patient prior to therapy should be maintained on treatment[b]
Response evaluation criteria: HI-E	
NTD (0 RBCs in 16 weeks) [a]	At least 2 consecutive Hb measurements ≥1.5 g/dL for a period of minimum 8 weeks in an observation period of 16 to 24 weeks compared with the lowest mean of 2 Hb measurements (apart from any transfusion) within 16 weeks before treatment onset[c]; only a response duration of at least 16 weeks, however, is considered clinically meaningful
LTB (3-7 RBCs in 16 weeks in at least 2 transfusion episodes, maximum 3 in 8 wk) [a]	HI-E in LTB patients corresponds to transfusion independence, defined by the absence of any transfusions for at least 8 weeks in an observation period of 16-24 weeks with the same transfusion policy (defined below) compared with 16 weeks prior to treatment; only a response duration of at least 16 weeks, however, is considered clinically meaningful
HTB (≥ 8 RBCs in 16 weeks, ≥ 4 in 8 weeks)	Major response: Major HI-E response in HTB patients corresponds to transfusion independence, defined by the absence of any transfusions over a period of minimum 8 weeks in an observation period of 16-24 weeks with the same transfusion policy (defined

Haematological improvement (IWG 2018)	**Response criteria (response must last at least 8 weeks)**
	below) compared with 16 weeks prior to treatment; only a response duration of at least 16 weeks, however, is considered clinically meaningful
	Minor response: Minor HI-E response in HTB patients is defined as a reduction by at least 50% of RBCs over a minimum of 16 weeks with the same transfusion policy (defined below) compared with 16 weeks prior to treatment
On-treatment RBC transfusion policy[d]	Transfusion policy for the individual patient prior to therapy should be maintained on treatment if not otherwise clinically indicated (documentation by the treating physician required); we suggest a maximum variation between pre- and on-study practice of 1 g/dL (or 0.6 mmol/L) in terms of transfusion threshold
Dose adjustment thresholds for high Hb levels	If the drug under investigation is stopped or its dose reduced in a responding patient for protocol-defined reasons leading to a loss of response, this should not be counted as such if reintroduction at the same or lower dose of the drug induces a new response; if reintroduction of the drug at a lower dose does not reinduce a response, this should be documented as such
Response evaluation criteria: HI-P	
Platelet response (pretreatment, $< 100 \times 10^9$/L	• Absolute increase of 30×10^9/L for patients starting with $> 20 \times 10^9$/L PLTs or • Increase from $< 20 \times 10^9$/L to $> 20 \times 10^9$/L and by at least 100% In addition, • Evolution of bleeding symptoms is to be taken into account • Increments of platelets also for patients with a pretreatment PLT count of $> 100 \times 10^9$/L are to be reported
Dose-adjustment policy for PLT counts on treatment	• If the drug under investigation is being stopped or its dose is being reduced in a responding patient for protocol-defined reasons leading to a loss of response, this should not be counted as such, if reintroduction at the same or lower dose of the drug induces a new response • When the investigational drug is stopped or reduced in dose, weekly blood counts are required to monitor the PLT levels • 2 subsequent PLT counts $> 450 \times 10^9$/L are a sufficient reason for treatment discontinuation in the case of treatment with TPO agonists
Response evaluation criteria: HI-N	
Neutrophil response (pretreatment, all patients)	At least 100% increase and an absolute increase $> 0.5 \times 10^9$/L (pretreatment, $< 1.0 \times 10^9$/L)
	Increments of neutrophils also for patients with a pretreatment ANC $> 1.0 \times 10^9$/L are to be reported

[a] HI-E achievement requires not only transfusion independence but also an increase of Hb by at least 1.5 g/dL (= 0.9 mmol/L).

[b] As in IWG 2006 criteria, only RBC transfusions administered for an Hb level below 9 g/dL are taken into account. Exceptions to this rule may be accepted in cases of well-documented moderate or severe angina pectoris, cardiac or pulmonary insufficiency, or ischemic neurologic diseases. In these cases, a higher transfusion trigger level may be established for an individual patient. These patients may require special attention when analysing responses within clinical trials. Transfusions for intercurrent diseases (bleeding, surgical procedure, etc) are not considered.

[c] Oscillations (eg, natural or due to drug intervals) within this period are accepted as long as the patient remains off any transfusions and the same transfusion policy has been maintained. We suggest accepting 1 drop to an increase of between 1.0 and 1.5 g/dL over a period of 8 wk. We recommend that intervals between blood counts do not exceed 2 wk.

[d] Exceptions to this rule may be accepted in cases of well-documented moderate or severe angina pectoris, cardiac or pulmonary insufficiency, or ischemic neurologic diseases. In these cases, a higher transfusion trigger level may be established for an individual patient. These patients may require special attention when analysing responses within clinical trials. Transfusions for intercurrent diseases (bleeding, surgical procedure, etc) should not be taken into account.

ANC, absolute neutrophil count; Hb, haemoglobin; HI-E, haematological improvement-erythroid; HI-N, haematological improvement-neutrophils; HI-P, haematological improvement-platelets; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion burden; NTB, not transfusion dependent; PLT, platelet; RBC, red blood cell; TPO, thrombopoietin.

P 3 References

Cheson et al 2006
Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108(2):419-25.

Platzbecker et al 2018
Platzbecker U, Fenaux P, Ades L, Giagounidis A, Santini V, van de Loosdrecht AA, et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. Blood 2019;133(10):1020-30.

Appendix Q Abbreviations

Abbreviation or special term	Explanation
ACTH	adrenocorticotropic hormone
AE	adverse event
AESI	adverse event of special interest
ALL	Acute Lymphoblastic Leukaemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
AML	Acute Myeloid Leukaemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase/transaminase
Bcl-2	B-cell lymphoma 2
Bcl-xL	B-cell lymphoma-extra large
BCRP	breast cancer resistance protein
BMMC	bone marrow mononuclear cells
BNP	brain natriuretic peptide
BP	blood pressure
CAR-T	chimeric antigen receptor T cell therapy
CBC	complete blood count
cfDNA	circulating free DNA
CLL	chronic lymphocytic leukaemia
C_{max}	maximum concentration
CMML	chronic myelomonocytic leukaemia
CMV	Cytomegalovirus
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CR	complete remission
CR_c	cytogenetic CR
CrCl	creatinine clearance
CR_i	complete remission with incomplete platelet recovery
CR_m	molecular CR
$CR_{MRD-NEG}$	CR with minimal/measurable residual disease negativity
$CR_{MRD-POS}$	CR with minimal/measurable residual disease positivity
CSP	Clinical Study Protocol

Abbreviation or special term	Explanation
CSR	Clinical Study Report
CT	computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumour DNA
CTEP	Cancer Therapy Evaluation Program
CYP	cytochrome P450
DCO	data cut-off
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DoR	duration of response
DUS	disease under study
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EoT	end of treatment
G6PD	Glucose-6-Phosphate-Dehydrogenase
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GVHD	graft versus host disease
HIV	human immunodeficiency virus
HL	Hy's Law
IA	interim analysis
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product

Abbreviation or special term	Explanation
INR	international normalisation ratio
IPSS-R	Revised International Prognostic Scoring System
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat
IV	intravenous(ly)
LDH	lactate dehydrogenase
LFT	liver function test
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
MLFS	morphologic leukaemia free state
MPN	myeloproliferative neoplasm
MRD	minimal/measurable residual disease
MRI	magnetic resonance image
MTD	maximum tolerated dose
mTPI-2	modified toxicity probability interval
MUGA	multigated acquisition
NCI	National Cancer Institute
NTproBNP	n-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	Pharmacodynamic
PEG	polyethylene glycol
PET	positron emission tomography
PHL	Potential Hy's Law
PI	Principal Investigator
PK	pharmacokinetic(s)
PR	partial remission
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 14 days

Abbreviation or special term	Explanation
RANKL	receptor activator of nuclear factor kappa-B ligand
RD	resistant disease
RNA	ribonucleic acid
RP2D	recommended Phase II dose
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Activities
SoC	standard of care
SRC	Safety Review Committee
TBL	total bilirubin
TD	target dose
TdP	Torsades de Pointes
TLS	Tumour lysis syndrome
TSH	thyroid-stimulating hormone
TTR	time to response
ULN	upper limit of normal
WHO	World Health Organization

Appendix R Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the TOC.

Amendment 2 [29 March 2022]

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

Overall Rationale for the Amendment:

The global protocol was amended to address comments received from various health authorities, ethics committees, and clarification requested from study sites. A summary of changes and the rationale for each change are tabulated below.

Section # and Name	Description of Changes	Brief Rationale	Substantial/ Non-substantial
2.1.1 Apoptosis and Cancer, 2.3 Study Rationale	Added background for high-risk MDS	To provide context for the inclusion of high-risk MDS patients in this study.	Substantial
4.5 Criteria for Stopping or Pausing Study Recruitment	Added a new section to describe the criteria for stopping or pausing study recruitment.	In response to HA/EC request to provide criteria for study-wide stopping or pausing study recruitment.	Substantial
5.1 Core Inclusion Criteria (#3, #6)	Included high-risk MDS, in Part A only (Criterion 3). Added Criterion 6 to specify that eligible high-risk MDS patients must have no available therapies to provide clinical benefit.	Patients with high-risk MDS are on a clinical continuum with AML with equally very poor prognosis and may also receive benefit from AZD0466.	Substantial
5.1 Core Inclusion Criteria (#5)	Criterion updated to clarify "for AML and ALL patients".	To clarify that inclusion criterion applies to AML and ALL patients; whereas for high-risk MDS patients, separate criteria and included in inclusion criterion 6.	Substantial
5.1 Core Inclusion Criteria (#9); *5.2 Core Exclusion Criteria (#4c*, #14*);* 6.5.1 Permitted Concomitant Medications and Treatments;	*Clarified hydroxyurea usage and patient population it should be used in and added high-dose steroid usage for white blood cell count control in patients with ALL and leukemia of ambiguous lineage. Also, specified the maximum dose and duration*	White blood cell count can fluctuate until the disease is under control. Therefore, treatment may be required during screening until the start of Cycle 2 to mitigate TLS risk. AML patients can be given hydroxyurea; *however, this is insufficient in ALL patients, for whom steroids are standardly used for control of high*	Substantial

Section # and Name	Description of Changes	Brief Rationale	Substantial/ Non-substantial
F2.3 Leukocyte Count	*of high-dose steroids allowed.*	*white blood cell counts. In addition, strict count-based rules for stopping hydroxyurea therapy result in implementation challenges due to expected fluctuations of the white blood cell counts.*	
5.2 Core Exclusion Criteria (#9) and 11.6.2.9.1 COVID-19 testing	Exclusion Criterion 9 was expanded to include details on study population inclusion based on COVID-19 history.	Expanded to allow inclusion of patients that have had a past infection but are still testing positive on sensitive PCR tests, which can remain positive for a long period of time despite not having an active infection. These patients must have a negative antigen test and presence of IgG antibodies.	Substantial
5.2 Core Exclusion (#20, #21)	Exclusion Criteria 20 and 21 were added to expand on populations excluded from participation.	Added in response to an EC request.	Substantial
5.2 Core Exclusion (#14); 6.5.2 Prohibited Concomitant Medications and Treatments	Revised text to state a maximum of 14 days washout periods for reversible CYP3A inhibitors and moderate or strong mechanism-based inhibitors or inducers of CYP3A4.	A duration of 14 days is considered an adequate washout period to account for any clinically relevant contribution from prescription or non-prescription small molecule drugs (including CYP3A inhibitors/inducers) to overall risk-benefit of AZD0466. Drug with half-life longer than 14 days (eg, isavuconazole) exhibit a biphasic plasma concentration-time profile, which results in significantly reduced systemic concentrations by Day 14 (post-dose) and therefore have a minimal impact on the risk-benefit of AZD0466.	Substantial
5.3 Lifestyle Considerations	Removed reference to “2” highly effective contraception.	As highly effective methods have less than 1% failure rate, it is not required to stipulate the number required.	Substantial
	Added text to indicate that male patients should use a condom with all sexual partners to avoid potential	To prevent exposure to a developing embryo.	

Section # and Name	Description of Changes	Brief Rationale	Substantial/ Non-substantial
	exposure to drug from the semen.		
6.6 Dose Modification and Toxicity Management	Added text and table for dose reduction (Table 4)	For clarification of dose reductions (see below).	Substantial
	Added text to indicate that patients diagnosed with COVID-19 while on study may continue if getting clinical benefit in the opinion of the investigator but must pause treatment if they meet pause or discontinuation criteria for dose modifications based on haematological parameters (Section 6.6.1, neutropenia), or CTCAE grade 2 or higher non-haematologic toxicities (Section 6.6.3), which would include pneumonia or other infectious complications.	COVID-19 language added in response to an EC request. If a patient is diagnosed with COVID-19 during treatment, but is deriving clinical benefit from the study treatment in the opinion of the Investigator, the patient may continue on study based on guidance provided in toxicity management therefore preventing patients discontinuing a potentially beneficial treatment.	

Section # and Name	Description of Changes	Brief Rationale	Substantial/ Non-substantial
6.6.1 Dose Modifications Based on Haematological Parameters; 6.6.2 Retreatment Criteria (Table 7); 6.6.3 Dose Modifications for Non-haematological Toxicities (Table 8); 6.6.4 Dose Modifications for Hepatotoxicity (Table 9); F1.2 AZD0466 Dose Modifications for TLS (Table 33)	Replaced % reductions by reductions based on previous dose levels and added dose modification guidelines during ramp up.	Alignment of dose modification guidelines with doses used in previous dose settings by replacing % reductions by reductions to lower doses; ie, '50% reduction' was replaced by ‘one lower dose’ and '75% reduction' was replaced by 'two lower doses'. This enables the patient to continue on a dose that has been considered safe in all cohorts. Avoids the use of intermediate doses that complicate dose findings.	Substantial
6.6.5 Cardiac Findings	Cardiac findings were clarified to specify that patients should not be discharged and continuously monitoring should be provided until patient is seen by a cardiologist for safety assessment.	In response to HA request for close and appropriate ECG monitoring (continuously) in hospital until a cardiologist’s opinion is issued for patients who discontinue treatment due to QT interval > 500 milliseconds.	Substantial
8.3.9 New Cancers	Changes made to regard as SAEs rather than AEs, and seriousness criteria clarified.	For clarification.	Substantial
8.7 Optional Genomics Initiative Sample	CCI [redacted]	CCI [redacted]	Non-substantial

Section # and Name	Description of Changes	Brief Rationale	Substantial/ Non-substantial
11.1.3.3 Dose Escalation, De-escalation, and Stopping Decision Rules	Removed the 3-day interval between dosing patient 1 at target dose (11 days from Day 1) and dosing subsequent patients in a cohort	Due to the rapidly progressive nature of relapsed/refractory acute leukemias, starting treatment as soon as possible after relapse is confirmed is highly important, as even small delays can lead to uncontrolled disease. A 3-day delay from target dose in patient 1 to enrollment of subsequent patients was incorporated as a conservative approach to address the unknown initial safety profile of the drug. In this study one key implication is that due to the dosing ramp-up during the first week, the delay between patient 1 and subsequent patients in a cohort is actually a total of 11 days (or more should the first patient not proceed with treatment as scheduled). While offering an incremental gain in safety data prior to dosing subsequent patients in the cohort, this delay puts subsequent patients at significant disadvantage should their disease progress.	Substantial
CCI [redacted]	[redacted]	[redacted]	[redacted]
11.3 Study Population – Module 1	Emphasized Core Inclusion Criterion 4.	In response to an HA request for clarity that patients must have exhausted standard of care prior to entering the study. No change was made to the inclusion criteria, but this item was highlighted wherever relevant in the protocol, to ensure it would not be missed.	Non-substantial
11.4.7.2 Dose Limiting Toxicity	Clarification to add COVID-19 as a documented infection due to active underlying disease will not be classified as a DLT.	To clarify that COVID-19 would be included as an infection.	Non-substantial
11.4.7.5 Maximum Feasible Dose	Added section defining maximum feasible dose.	For clarification of the Chemistry Manufacturing and Controls (CMC) quality specifications, which is	Non-substantial

Section # and Name	Description of Changes	Brief Rationale	Substantial/ Non-substantial
		currently set against a maximum weekly dose of 3600 mg.	
11.5.1 Schedule of Activities (Table 25)	CCI [redacted]	CCI [redacted]	Non-substantial
11.5.1 Schedule of Activities (Table 17); 11.6.2.9.8 Cardiac Troponin and BNP (or NTproBNP); 12.5.1 Schedule of Activities (Table 25); 12.6.2.9.8 Cardiac Troponin and BNP (or NTproBNP)	Removed the Cycle 1 Day 8 assessment of cardiac troponin I. Revised text/footnote to indicate that troponin I is preferred but troponin T is acceptable if troponin I is not available at the site.	The Sponsor's cardiology experts have confirmed that both troponin I and troponin T are acceptable to assess acute cardiac abnormalities. Therefore, language changed to clarify that troponin I highly preferred, however troponin T acceptable if sites do not have access to troponin I testing. However, at any abnormal troponin result, further investigations required. Troponin to be evaluated at screening (to obtain a baseline value) and as clinically indicated thereafter.	Substantial
11.5.1 Schedule of Activities (Table 15); 11.6.2.6 Electrocardiograms; 12.6.2.6 Electrocardiograms	Replaced single safety ECG option at Holter visits with triplicate ECGs requirement at all ECG-required visits. In addition, revised footnote (Table 15) to indicate that on PK sampling visits, triplicate ECGs will be collected prior to PK sampling.	Holter recordings will not show instant ECG values, which are required prior to infusion. Triplicate ECG is more appropriate to identify any abnormal values prior to infusion decision.	Non-substantial
11.5.1 Schedule of Activities (Table15); 11.6.2.9.12 Overnight Stays for TLS Monitoring	Added text to indicate that patients may be discharged prior to 24 hours post-dose if they are able to complete required safety and laboratory assessments within the specified time windows.	This update was made to allow flexibility for reducing in-patient stays, as long as required safety evaluations are performed. White blood cell parameters remain in place to ensure all enrolled patients are at low risk for TLS. No SAEs associated with tumor lysis occurred in the 300 mg cohort.	Substantial
11.6.1.4 Minimal/ Measurable Disease (Part B Only); Appendix J Response Evaluation Criteria	Added text to indicate that MRD negative or positive status (or conversion from negative to positive MRD) will need to be confirmed with a second MRD negative	For clarification.	Non-substantial

Section # and Name	Description of Changes	Brief Rationale	Substantial/ Non-substantial
for Acute Myeloid Leukaemia (Table)	or positive sample devoid of blasts obtained within the interval specified, and that MRD status of patients will be monitored every 3 cycles (or at the discretion of the Investigator, in line with scheduled response assessments) thereafter.		
11.6.2.9.2 Viral Serology; 12.6.2.9.2 Viral Serology	Added the following text: "If a patient was found to have positive anti-HBc antibody and a negative HBsAg, a DNA PCR test will be done to determined eligibility criteria."	Clarification to distinguish patients who have prior versus active infection and no undetected active disease at enrolment.	Non-substantial
11.6.2.9.4 Clinical Chemistry; 12.6.2.9.4 Clinical Chemistry	Revised text to indicate that if an unscheduled ECG is performed, an electrolyte panel (ie, calcium, magnesium, potassium) must be done and troponin performed as clinically indicated to coincide with the ECG assessment, and referral to a cardiac specialist if required.	Rephrased sentence for clarity.	Non-substantial
11.6.3.1.1 Blood Sample for Plasma Pharmacokinetics; 12.6.3.1.1 Blood Sample for Plasma Pharmacokinetics	Added the following text: "including if central line access is available".	For clarification of how PK samples should be taken, to avoid sampling artifacts	Non-substantial
11.6.3.1.1 Blood Sample for Plasma Pharmacokinetics; 12.6.3.1.1 Blood Sample for Plasma Pharmacokinetics	Added "as close to the end of the infusion, but permissible up to 10 minutes" for the sample collected at the end of the infusion.	To better characterize maximum plasma concentration.	Non-substantial
11.6.3.1.3 Blood Samples for Metabolite Identification	Removed sample collection on Cycle 1 Days 1, 4, 9, 10, and 11 and Cycle 2 Day 2.	To reduce patient burden and it is unnecessary to obtain so many samples for metabolite identification.	Non-substantial

Section # and Name	Description of Changes	Brief Rationale	Substantial/ Non-substantial
11.6.3.2.2 and 12.6.3.2.2 Pharmacodynamic [redacted]	Added assessment timepoints to table.	To better characterise the PD response in patients, aligning collections to PK timepoints.	Non-substantial
11.6.5.1 [redacted]	[redacted]	[redacted]	Non-substantial
12.6.2.9.12 Overnight Stays for TLS Monitoring	Added PK assessments as part of the rationale for in-patient treatment administration.	For clarification that patients have frequent PK sampling during Module 2, therefore preventing discharge over night	Non-substantial
12.7.2 Sample Size Determination	Updated text from a sample size determined empirically to that based on statistical criteria.	To provide statistical justification of sample size based on within-subject coefficients of variation/power calculations.	Non-substantial
12.7.3 Populations for Analysis	Clarified that pharmacokinetic population will include subjects with "at least one" reportable plasma concentration	To be more specific with description of the population	Non-substantial
Appendix I2 (Table 37)	Updated table footnotes.	For clarification.	Non-substantial
Appendix O Prognostic Scoring for Myelodysplastic Syndrome; Appendix P Response Criteria for Myelodysplastic Syndrome	Added prognostic and response criteria for MDS.	These criteria were added given that patients with MDS are now eligible for enrolment in this study.	Substantial
Not applicable	Minor editorial changes were made to the document, to correct formats and spelling, to clarify protocol instruction, and to align text with related sections of the protocol		Non-substantial

Amendment 1 [14 July 2021]

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

Overall Rationale for the Amendment:

The global protocol was amended to address comments received from various health authorities, ethics committees and clarification requested from study sites. A summary of changes and the rationale for each change are tabulated below.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Synopsis, 2 Introduction – Core, 2.3 Study Rationale, 4.1 Overall Design, 4.2.1 Regulatory Amendments for Additional Modules, 6.1 Study Treatment(s) Administered	This section was updated with text regarding potential for 4 additional modules to the study where permissible by local regulations.	Text was added regarding the potential additional of modules to the protocol, to further support the scientific rationale and the overall goal of the study to generate clinically meaningful data - including combination therapies - which in turn would guide the course of development of AZD 0466. A caveat was added that these modules maybe added only if permissible by local regulations.	Non-substantial
2.1.2 Rationale for AZD0466 in treatment of haematological malignancies	Text regarding ongoing study D8240C00003 was updated	The D8240C00003 study has now changed status (enrolment complete), hence the referring text was updated in this protocol amendment.	Non-substantial
4.4 End of Study Definition	This section was updated with definitions of End of Module and with a plan for reporting results for each module, as well as after the final study analyses for all modules.	These updates were of an administrative nature.	Non-substantial
5.1 Core Inclusion Criteria	Inclusion criterion 2 was edited to clarify that subjects who are 18 years of age in some countries may be eligible for the study, but may need to sign assent forms,	This clarification was added to accommodate countries where 18 years may be below the age limit for consent.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	together with parental consent forms.		
	Inclusion criterion 4 was updated to clarify that eligible patients must not have an established standard of care with proven benefit at the time of enrolment	This clarification was provided in response to query from South Korean Ministry of Food and Drug Safety (MFDS).	Non-substantial
	Inclusion criterion 7 was updated to reduce the predicted life expectancy of eligible patients from 12 weeks to 8 weeks.	This inclusion criterion was updated in line with realistic clinical characteristics seen in patients with leukaemia.	Substantial
	Inclusion criterion 9 was edited to omit the eligibility requirement of the absence of a prior history of pancreatitis, and add a requirement of absence of clinical pancreatitis at the time of enrolment.	This inclusion criterion was updated in line with realistic clinical characteristics seen in patients with leukaemia.	Substantial
	The exclusion criterion about reproduction was updated to clarify that women of childbearing potential must be willing to use highly effective contraceptive measured, and that they should have a negative serum pregnancy test.	These updates were made for clarity, and consistency with Section 5.3 of this protocol.	Non-substantial
5.2 Core Exclusion Criteria	Exclusion criterion 3 was corrected to exclude patients with a history of haematopoietic stem cell transplantation within 100 days prior to the first dose of study treatment.	This exclusion criterion was updated to provide more clarity on the eligibility of patients with a history of haematopoietic stem cell transplantation.	Substantial
	Exclusion criterion 4 was updated to clarify eligibility requirements amongst patients receiving immunosuppressants for graft versus host disease (GVHD) and primary malignancy control.	This exclusion criterion was updated to provide more granularity about terms of exclusion of patients taking immunosuppressants for GVHD and primary malignancy control.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	Exclusion criterion 8 was edited to clarify that patients with known uncontrolled cytomegalovirus (CMV) infection will be excluded from the study.	This exclusion criterion was updated to remove the eligibility testing requirement for CMV infection, and to clarify that subjects with known active CMV infection will be excluded.	Non-substantial
	Exclusion criterion 11 was updated to 1. add the New York Heart Association (NYHA) Functional Classification for the assessment of cardiac eligibility criteria 2. allow for investigator discretion in assessing the eligibility of abnormalities in electrograms (ECGs) 3. edit the risk of arrhythmic events to omit heart failure and hypokalaemia	This exclusion criterion was updated to add a standardised method for the testing of cardiac eligibility criteria and provide clarity on how risk assessment will be done for abnormalities in rhythm and arrhythmic events.	Substantial
	Exclusion criterion 12 was updated to clarify that patients with a history of myelodysplastic syndrome or myeloproliferative neoplasm (including chronic myelomonocytic leukaemia [CMML]), **will be eligible** for enrolment in this study.	This exclusion was updated to clarify that the exclusion criterion of "history of life-threatening malignancy ≤ 2 years prior to first dose of study treatment" did not apply to myelodysplastic syndrome or myeloproliferative neoplasm.	Substantial
	In exclusion criterion 13, the exclusion conditions of prior or concomitant congestive heart failure, ventricular arrythmias and supraventricular arrythmias were omitted.	This exclusion criterion was updated because it was repetitive of the cardiac criteria in #11.	Non-substantial
	Exclusion criterion 14 was updated to clarify that patients	This exclusion criterion was edited to make it	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	receiving high dose steroids for primary malignancy control would be eligible if these steroids are discontinued 2 days before the first dose of study treatment.	consistent with the conditions for high dose steroid use in exclusion criterion 4.	
	Exclusion criterion 14 was also updated to provide more detail on the allowable use of hydroxyurea until the start of cycle 2, and direction about therapy discontinuation at least 7 days prior to the first dose of study treatment for patients who relapse while on maintenance therapy.	This exclusion criterion was edited to provide more detail and clarity on the use of these concomitant drugs.	Substantial
	Exclusion criterion 14 was also updated to provide clearer direction about exclusion of subjects for whom the following types of medications cannot be discontinued within 5 half-lives of the first dose of study treatment, and withheld until 14 days after the last dose of AZD0466: 1. reversible cytochrome P450 3A (CYP3A) inhibitors, 2. sensitive substrates of BCRP, OCT2, OAT3, OATP1B1, OATP1B3, CYP2B6, CYP2C8, CYP2C9, or CYP2D6, or 3. moderate or strong mechanism-based inhibitors or inducers of CYP3A4 4. medications with known risk of Torsades de Pointes.		
	Exclusion criterion 14 was also updated to clarify that heparin required for vascular	This exclusion criterion was edited to add more detail and clarity on the	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	line management was not an exclusion criterion.	concurrent use of anticoagulants.	
5.3 Lifestyle Considerations	This section was updated to clarify that male patients with a partner of non-child bearing potential should use a condom for 35 days after the last dose of study treatment.	This exclusion criterion was edited to add more clarity on the required time period for the use of condoms in this study	Non-substantial
5.4 Screen Failures and 8 Study Assessments and Procedures – Core, Appendix A3 Informed Consent Process, Appendix M1 Rescreening of Participants to Reconfirm Study Eligibility	This section was updated to clarify that patients who fail screening may be re-screened up to 2 times for study eligibility.	This text was edited to add an allowance of up to 2 re-screening per patient.	Non-substantial
6.5.1 Permitted Concomitant Medications and Treatments	This section was edited to clarify that allopurinol must be used for tumour lysis syndrome (TLS) prophylaxis per institutional guidelines	This text was edited to clarify the terms of allopurinol use in the study.	Non-substantial
	This section was also edited to clarify that patients who get vaccinated for Coronavirus disease 2019 (COVID-19) must do so at least 7 days before the first dose of study treatment, where possible.	This text was updated to add COVID-19 vaccine language to permitted medications	Non-substantial
6.5.2 Prohibited Concomitant Medications and Treatments	The table listing strong inducers of CYP3A, moderate inducers of CYP3A and mechanism-based strong inhibitors of CYP3A was updated with new drugs enasidenib and midostaurin ivosidenib.	This table was updated with drugs which were likely prescribed to patients who would be eligible for the study	Non-substantial
6.6.1 Dose Modifications Based on Haematological Parameters	The recommended dose modifications for haematological changes of toxicity grade “Grade 3 or 4 neutropenia” and “Febrile neutropenia/neutropenic	This section was updated to reflect clinical practice in patients with neutropenia, in discussion with lead investigator.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	infection (any grade lasting > 2 days)" were replaced by new recommendations with updated actions in an added row "Grade 4 neutropenia, with or without fever or infection". The absolute neutrophil count (ANC) threshold was reduced from > 1.0×10^9/L to ≥ 0.5×10^9/L		
6.6.3 Dose Modifications for Non-haematological Toxicities	It was specified that non-haematological toxicities will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5	The CTCAE criteria version was added for clarity.	Non-substantial
6.6.5 Cardiac findings	This section was updated to add that AZD0466 should be permanently discontinued if a CTCAE ≥ Grade 3 cardiac adverse event (AE) of any duration occurs during study treatment, if considered by the Investigator to be related to study treatment.	This section was updated with more specific treatment discontinuation criteria in patients with cardiac findings.	Substantial
6.6.6 Infusion-site reactions	This section was added with guidance about drug interruption in the event of infusion site reactions	This section was added to guide the investigator with specific criteria for management of infusion site reactions.	Substantial
8.3.13.2 Paternal Exposure	This section was edited to clarify that the outcome of all pregnancies occurring from the date of first dose and for 35 days after the last dose of study treatment, plus 6 months, should be documented.	This section was edited to make the language for pregnancy follow-up clearer.	Non-substantial
8.6.1.1 CCI [redacted]	CCI [redacted] .	CCI [redacted]	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
9.7.1 Adverse Events	The defined follow-up period for AEs was changed from 30 days to 28 days.	This section was edited to keep it consistent with the time period and frequency for collecting AE and serious adverse event (SAE) information in Section 8.3.1.	Non-substantial
10 REFERENCES - CORE	A new reference “Ji et al 2010 Ji Y, Liu P, Li Y, B, Bekele N. A modified toxicity probability interval method for dose-finding trials. Clin Trials. 2010;7(6):653-63.” was added	A new reference used to update text in this protocol amendment was added.	Non-substantial
11.1.3.1 Justification for Starting Dose and 11.4.1 Study Treatment – AZD0466	This section was updated with text from the ongoing study D8240C00003 (that AZD0466 200 mg intravenous (IV) is tolerated in patients with advanced solid malignancies, and that the study has completed recruitment) and by making the text about dose ramp-up on Day 1 and Day 4 consistent with Figure 3. Section 11.4.1 was also updated with the text about dose ramp-up.	This text was edited to clarify the planned dose ramp-up in the protocol.	Non-substantial
11.1.3.3 Dose escalation, de-escalation, and stopping decision rules	This section was edited to clarify that the decisions on dose escalation were based on outcomes from an internal AZ simulation package, the operating characteristics of which were also added to the protocol in Table 10.	This change was made in response to a site query for clarity regarding operating characteristics on the mTPI-2 design.	Non-substantial.
11.3 STUDY POPULATION - MODULE 1 and 12.3 STUDY POPULATION - MODULE 2	A note was added that each patient may only be enrolled in one module of this study. A patient who enrols in one module of this study is not eligible to participate in another module.	These sections were updated to make explicit that a patient who has participated in one module of this study cannot then participate in another.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
11.4.7.2 Dose-limiting Toxicity	This section was updated to add more detail on what would be considered a dose-limiting toxicity (DLT) in this study, to specify that AZD0466 should be permanently discontinued if a drug-related CTCAE Grade ≥ 3 cardiac AE of any duration occurs at any time during study treatment, and to define the period of DLT evaluation.	This section was updated to refine the definition and actions taken with dose-limiting toxicity in this study, and to keep consistency with Section 11.4.7.1.	Substantial
11.4.7.3 Definition of Maximum Tolerated Dose	This section was updated with the rules for 2 or more tied doses that are equidistant from the target toxicity dose of 30%.	This update was made in order to take a more conservative approach if the estimated DLT rate for the tied doses are a combination of < 30% and > 30%.	Substantial
Table 15: Module 1 - Schedule of Activities for Screening and Cycle 1 (Parts A and B)	Footnote a was added in the ramp-up 2 column to allow for visits to be conducted over the telephone if it does not require attendance for blood draws or physical examination	This footnote was added to allow for flexibility in the study, where site visits are not required.	Non-substantial
	Footnote b was added to the cycle 1 visit window row to clarify that the Days 1, 4 and 8 ramp-up dose administration should be at least 72 h apart.	This footnote was added to clarify that dose ramp-ups should be no more frequent than 72 hours to allow for a suitable safety assessment.	Non-substantial
	Footnote c was added to the Chest X-ray row to note that Chest X-rays may also be performed at other timepoints during the study at the Investigator's discretion, when clinically indicated.	This update was made in response to a query from the South Korea MFDS.	Non-substantial
	Day 8 assessments were marked, and Day 11 assessments deleted for cardiac troponin and brain natriuretic peptide (BNP) (or n-terminal pro b-type natriuretic peptide	The schedule of assessments for cardiac troponin and BNP (or NTproBNP) was updated to evaluate cardiac troponin levels before	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	[NTproBNP]). The associated footnote j was also updated to add that cardiac troponin samples on Day 8 should be collected pre-infusion, and may be collected at other timepoints in the study if clinically indicated.	patients receive the target dose on Day 8.	
	Footnote k was added to the serum immunoglobulins row to clarify that a routine serum immunoglobulin profile (IgA, IgG, IgM) would be assessed.	This footnote was added for clarity about the serum immunoglobulin assessments.	Non-substantial
	Footnote l was added to the pharmacokinetic (PK) assessments row to refer to Section 11.6.3.1 for information on timepoints for PK assessment.	This footnote was added for clarity about PK assessment timepoints.	Non-substantial
	It was clarified that blood CCI [redacted] will be collected at disease assessment (Part A and B) and minimal/measurable residual disease (MRD) timepoint in Part B. Footnote n was added to the Table with this instruction.	The schedule of assessments CCI [redacted] was updated to enable an analysis of orthogonal biomarkers on biospecimen collected at the same time.	Substantial
	The collection of blood CCI [redacted] using plasma and serum was omitted from this table.	This previously planned assessment has now been omitted from the study.	Non-substantial
	CCI [redacted]	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
		CCI [redacted]	
	Footnote o was updated to note that the window for bone marrow biopsy at screening is 28 days, and that when it is not possible to obtain a bone marrow biopsy sample, a historic bone marrow biopsy sample may be used.	The allowance and acceptable window for a historic bone marrow biopsy sample was added for screening.	Substantial
Table 16: Module 1 - Schedule of Activities for Treatment Cycle 2 and Beyond and Follow-up Periods (Part A and B)	All assessments for cardiac troponin and BNP (or NTproBNP) from Cycle 2 and beyond were deleted. It was specified that troponin may be assessed at investigators' discretion (throughout the study period, including Cycle 2 and beyond).	The schedule of assessments for cardiac troponin and BNP (or NTproBNP) was updated for evaluation prior to getting the target dose a Cycle 1 Day 8, and thereafter at any other timepoint through the study at the Investigator's discretion.	Substantial
	The rows for blood CCI [redacted] analysis were updated with assessments at each disease assessment (Part A and B)/MRD timepoint (Part B). Footnote f was added to the Table with this instruction. CCI [redacted]	The schedule of assessments for CCI [redacted] was updated to enable an analysis of CCI [redacted] biomarkers on biospecimen collected at the same time.	Substantial
	An MRD assessment for Part B (expansion) was deleted at	The schedule of assessments for MRD assessments was updated	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	Cycle 1 Day 1 and added at the EoT visit.	to clarify that a bone marrow sample will not be collected on Cycle 1 Day 1.	
11.6.1.3 Bone Marrow and 12.6.1.3 Bone Marrow	These sections were updated to allow for a historic bone marrow biopsy sample if an eligible patient is unable to give a fresh bone marrow biopsy sample due to extenuating circumstances, with the approval of the Medical Monitor.	The allowance and acceptable window for a historic bone marrow biopsy sample was added for screening.	Substantial
	These sections were also updated to clarify that the window for these screening assessments is 28 days.	This section was updated to make the screening window for all screening assessments consistent.	Non-substantial
11.6.1.4 Minimal/Measurable Residual Disease (Part B Only)	An MRD assessment for Part B (expansion) was deleted at Cycle 1 Day 1 and added at the end of treatment (EoT) visit. It was also clarified that MRD assessments will be made at any morphologic remission timepoint, and that patients with confirmed CR without measurable residual disease (CR_{MRD}) will be monitored every 3 cycles, and thereafter until disease progression, per the investigator's discretion.	This section was updated with text for MRD assessments at any morphological remission timepoint, and in patients with confirmed CR_{MRD}, up to 2 years after CR_{MRD} confirmation, at the discretion of the Investigator.	Substantial
11.6.2.1 Physical Examination	This section was updated to clarify that physical examination will be done pre-infusion and on the calendar day after the dosing day during each cycle.	The text for the schedule of assessments for physical examination in this study was clarified.	Non-substantial
11.6.2.4 Chest X-ray and 12.6.2.4 Chest X-ray	These sections were updated to add that a Chest X-ray may also be performed at other timepoints during the study at the Investigator's discretion, when clinically indicated.	This update was made in response to a query from the South Korea MFDS.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
11.6.2.5 Vital Signs and 12.6.2.5 Vital Signs	These sections were updated to clarify that temporal instead of oral temperature assessment will be done, and that blood pressure (BP) and pulse measurements may be made in a seated position.	These sections were updated to provide new guidance on vital sign assessments at the sites.	Non-substantial
11.6.2.6 Electrocardiograms and 12.6.2.6 Electrocardiograms	These sections were updated by replacing a bullet pointed list of assessments timepoints with a tabulated list of ECG assessment timepoints, and to clarify that Day 1 pre-infusion and end of infusion ECGs will be conducted during each cycle. Section 12.6.2.6 for Module 2 ECG assessments was updated with additional ECG timepoints (Cycle1 Period 3 Days 17 and 18).	This update was made for better presentation of ECG assessments The additional ECG timepoints (Cycle1 Period 3 Days 17 and 18) were added to Module 2 for safety monitoring after infusion of target dose of AZD0466 in combination with voriconazole.	Non-substantial
11.6.2.6.1 Continuous 12-lead ECG Recordings (Holter)	It was clarified that continuous recordings of 12-lead ECGs will be performed for the purpose of PK modelling, which in turn would allow for monitoring of PR, QRS, QT, QTcF, RR intervals.	This section was updated to provide clarification on the purpose of continuous 12-lead ECG Recordings	Non-substantial
Table 18 Clinical Chemistry and Table 26 Clinical Chemistry	Footnote b was added to each table clarify that glutamate dehydrogenase testing is optional, but should be performed where sites have the capability to perform the test locally.	The clinical chemistry table was modified to reflect the test as not mandatory, but optional, given the exploratory nature of the glutamate dehydrogenase testing.	Substantial
11.6.2.9.8 Cardiac troponin and BNP (or NTproBNP) and 12.6.2.9.8 Cardiac troponin and BNP (or NTproBNP)	This section was updated to add that cardiac troponin and BNP (or NTproBNP) samples on Day 8 should be collected pre-infusion, to omit all planned assessments during Cycle 2 and every 3 cycles	The schedule of assessments for cardiac troponin and BNP (or NTproBNP) was updated for evaluation prior to getting the target dose a Cycle 1 Day 8. Thereafter	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	thereafter, and to add that cardiac troponin I samples may be collected at other timepoints in the study if clinically indicated.	Troponin can be assessed at investigators' discretion (throughout the study which includes Cycle 2 and beyond).	
	These sections were also updated to clarify that isolated troponin elevations are not sufficient to trigger dosing changes and should be evaluated in the context of other cardiac findings.	This update was made for patient safety purposes, and to provide additional guidance on dose changes due to elevated cardiac troponin levels.	Substantial
11.6.2.9.9 Cortisol, ACTH and TSH, 11.6.2.9.10 Serum immunoglobulins, and 11.6.2.9.11 Urinalysis 12.6.2.9.9 Cortisol, ACTH and TSH, 12.6.2.9.10 Serum immunoglobulins, and 12.6.2.9.11 Urinalysis	These sections were updated to clarify that the window for these screening assessments is 28 days.	This section was updated to make the screening window for all screening assessments consistent.	Non-substantial
11.6.2.9.12 Overnight stays for TLS monitoring and 12.6.2.9.12 Overnight stays for TLS monitoring	These sections were updated to clarify that Overnight stays will be recommended, instead of mandatory, for dosing on Days 15, 22, and 29 during Module 1 Cycle 1 and Day 15 Cycle 1 (Period 3) and Cycle 2 for Days 1 and 8 during Module 2, allowing for patients to be discharged prior to 24 hours post-dose as per Investigator discretion, and with planned clinic follow-up within 12 hours after discharge, if their TLS laboratory values are appropriate.	This update was made to allow flexibility for reducing inpatient stays beyond the first 3 doses in Cycle 1, per the Investigator's discretion.	Substantial
	These sections were also updated to clarify that TLS monitoring should be	This update was made to clarify that TLS monitoring should be	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	performed (as specified in Table 15 for Module 1 and Tables 23 and 24 for Module 2) at least as frequently as every 12 hours during the first 24 hours after each administration of study treatment, and thereafter as clinically indicated.	done at least once every 12 hours instead of twice every 24 hours, which may be ambiguous.	
11.6.3.1.1 Blood Sample for Plasma Pharmacokinetics	In Section 11.6.3.1.1 the table for blood samples for plasma PK was updated with a footnote referring the reader to Section 11.6.2.6 for ECGs measured at matched PK timepoints.	This update was administrative, and was made to refer the reader to a related section of the protocol.	Non-substantial
11.6.3.1.1 Blood Sample for Plasma Pharmacokinetics and 12.6.3.1.1 Blood Sample for Plasma Pharmacokinetics	A new footnote was added to the Table for Blood Sample for Plasma PK, at the 9 hour post-infusion timepoint on Cycle 1 Day 8 (Module 1) and the 9 hour post-infusion timepoint on Cycle 1 Period 3 Day 15 (Module 2), to clarify that if a planned collection is no longer possible at the scheduled timepoint, the Medical Monitor must be informed, and any collection outside allotted window must be discussed with the Medical Monitor	This footnote was added to provide flexibility and guidance around this blood collection timepoint.	Non-substantial
11.6.4.1.1 CCI	CCI	CCI	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	CCI		
CCI			
CCI			
11.6.4.1.6 Bone marrow biopsy and aspirate CCI CCI and 12.6.4.1.3 Bone marrow biopsy and aspirate CCI CCI	This section was updated to clarify that bone marrow biopsy samples will be collected in accordance with local/institutional guidelines and as per the process delineated in the laboratory manual.	This update was made to clarify that local/institutional guidelines will be used to conduct bone marrow biopsies and aspirate, but using a process delineated in the laboratory manual.	Non-substantial
11.7.6 Efficacy	This section was updated to omit the word "programmatically" when speaking of assigning a response of complete remission (CR), CR with incomplete platelet recovery (CR_i), morphologic leukaemia free state (MLFS), partial	This update was made because a response of CR, CR_i, MLFS, PR, CR_c, CR_m, Relapse or Failure is not being assigned programmatically	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	remission (PR), Cytogenetic CR (CR_c), Molecular CR (CR_m), Relapse or Failure		
12.1.5 Module 2 Study Design	The dose ramp-up schedules in Periods 1, 2 and 3 were updated.	This update clarified the schedule and strategy for dose ramp-ups during Module 2.	Non-substantial
12.3.2 Exclusion Criteria	This section was updated to add an exclusion criterion for Module 2, making patients for whom voriconazole is contraindicated ineligible for the study.	Module 2 investigates a potential drug-drug interaction between AZD0466 and voriconazole, hence patients for whom voriconazole is contraindicated cannot participate in the study.	Non-substantial
Table 23: Module 2 - Schedule of Activities for Screening and Cycle 1	Footnote a was added in the ramp-up 2 column to allow for visits to be conducted over the telephone if attendance for blood draws or physical examination is not required	This footnote was added to allow for flexibility in the study, where site visits are not required.	Non-substantial
	Footnote c was added to the Chest X-ray row to note that Chest X-rays may also be performed at other timepoints during the study at the Investigator's discretion, when clinically indicated.	This update was made in response to a query from the South Korea MFDS.	Non-substantial
	Day 8 assessments were marked, and Day 11 assessments deleted for cardiac troponin and BNP (or NTproBNP). The associated footnote g was also updated to add that cardiac troponin samples on Day 8 should be collected pre-infusion, and may be collected at other timepoints in the study if clinically indicated.	The schedule of assessments for cardiac troponin and BNP (or NTproBNP) was updated for evaluation prior to getting the target dose a Cycle 1 Day 8, and thereafter at any other timepoint through the study at the Investigator's discretion	Substantial
	Footnote i was updated to note that the window for bone	The allowance and acceptable window for a	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	marrow biopsy at screening is 28 days, and that when it is not possible to obtain a bone marrow biopsy sample, a historic bone marrow biopsy sample may be used.	historic bone marrow biopsy sample was added for screening.	
Table 24: Module 2 - Schedule of Activities for Cycle 2 and beyond	Visit windows were added to this table.	This table was updated with clarity about the visit windows	Non-substantial
	All assessments for cardiac troponin and BNP (or NTproBNP) from Cycle 2 and beyond were deleted. It was specified that troponin may be assessed at investigators' discretion (throughout the study period, including Cycle 2 and beyond).	The assessments for cardiac troponin and BNP (or NTproBNP) will now be done at any timepoint through the study at the Investigator's discretion.	Substantial
	An MRD assessment for Part B (expansion) was deleted at Cycle 1 Day 1 and added at the EoT visit.	The schedule of assessments for MRD assessments was updated during this amendment.	Substantial
12.6.2.9.6 Complete blood count with differential including CCI	This section was updated with wider widows (30 minutes instead of 15 minutes) for blood collection at the Cycle 1 Period 1 Day 8, 2 hours post-dose timepoint, and the Cycle 1 Period 3, Day 15, 2 hours post-dose timepoint.	This change was made for consistency with the 2-hour timepoint in Section 11.6.2.9.6.	Non-substantial
Appendix F 1.1 Prophylaxis for TLS	This Appendix was updated to add more detail about specific recommendations for prophylaxis for TLS with regard to IV hydration and allopurinol use, but to clarify that details of TLS management may vary per institutional practice, .	This Appendix was updated to provide additional detail regarding TLS prophylaxis, but also allow flexibility per institutional practice.	Non-substantial
Appendix F 1.2 AZD0466 Dose Modifications for TLS	Table 31 AZD0466 Dose Modifications for TLS was updated to clarify that AZD0466 may be delayed up to 7 days if an abnormal	This section was edited to align with clinical practice in the management of TLS in low or intermediate risk	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	laboratory finding is present before study drug administration. The laboratory value for abnormal phosphate levels was changed to "Phosphate ≥ 1.6 mmol/L (5.0 mg/dL) (0.5 mg/dL) increase", with an added note that in the event of an isolated phosphate abnormality, restarting the dose may be discussed with the Medical Monitor. Two references to support these changes were added to the footnote. The rows for "Abnormality (present before admin of AZD0466)" were deleted.	leukaemia patients, and to allow for flexibility due to patient variability.	
Appendix F 2.3 Leucocyte Count	Text regarding prior cytotoxic chemotherapy was omitted and the following statement was added: Treatment with low dose prednisone (10 mg or less) or equivalent dose of alternative steroid is permitted. Treatment with high-dose steroids for primary malignancy control is permitted, but must be discontinued at least 2 days prior to the first dose of study treatment.	This appendix was updated to align text about treatment with low dose prednisone with clinical practice, where steroid use is permissible for disease control - but other cytotoxic agents would be considered new treatment.	Non-substantial
Appendix G Classification of Tumour Lysis Syndrome	In Table 33 Criteria for Laboratory and Clinical Tumour Lysis Syndrome, the criteria for hyperphosphataemia was corrected from 1.5 to 4.5 mg/dL.	This edit was a correction.	Non-substantial.
Appendix H: Drugs That Prolong QT Interval and/or Induce Torsades De Pointes	It was clarified that drugs with a known risk of Torsades de Pointes should be withheld for 5 half-lives prior to the first dose of study treatment and	This section was updated to provide clarity for the study sites regarding the restricted use of drugs that	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	for 14 days after the last. A tabulated list of drugs with a known risk of Torsades de Pointes was added.	have a known risk of Torsades de Pointes .	
Appendix J: Response Evaluation Criteria for Acute Myeloid Leukaemia	The table for response evaluation criteria in this appendix was replaced by revised recommendations, with categories of response, treatment failure and relapse. All irrelevant literature references were deleted.	In this appendix response criteria were updated to reflect current guidelines, and to address internal inconsistencies	Non-substantial
Appendix N: New York Heart Association Functional Classification	This new appendix was added to support the exclusion criterion of patients with a history of myocarditis or heart failure NYHA Functional Classification Class 3 or 4.	This new appendix was added to support a cardiac eligibility assessment	Non-substantial
NA	Minor editorial changes were made the document, to correct formats and spelling, to clarify protocol instruction and to align text with related sections of the protocol		Non-substantial

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