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Golidocitinib (AZD4205)

Document Type:	**Statistical Analysis Plan**
Protocol Number:	**DZ2019J0005**
NCT Number:	**NCT04105010**
Document Date:	**March 25, 2023**

A Phase I/II, Open-Label, Multicentre Study to Investigate the Safety, Tolerability, Pharmacokinetics and Anti-tumor Activity of AZD4205 in Patients with Peripheral T Cell Lymphoma (PTCL) (Part B only)

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Statistical Analysis Plan

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Document Version: Version 3.0

Document Date: March 25, 2023

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Sponsor: Dizal (Jiangsu) Pharmaceutical Co., Ltd

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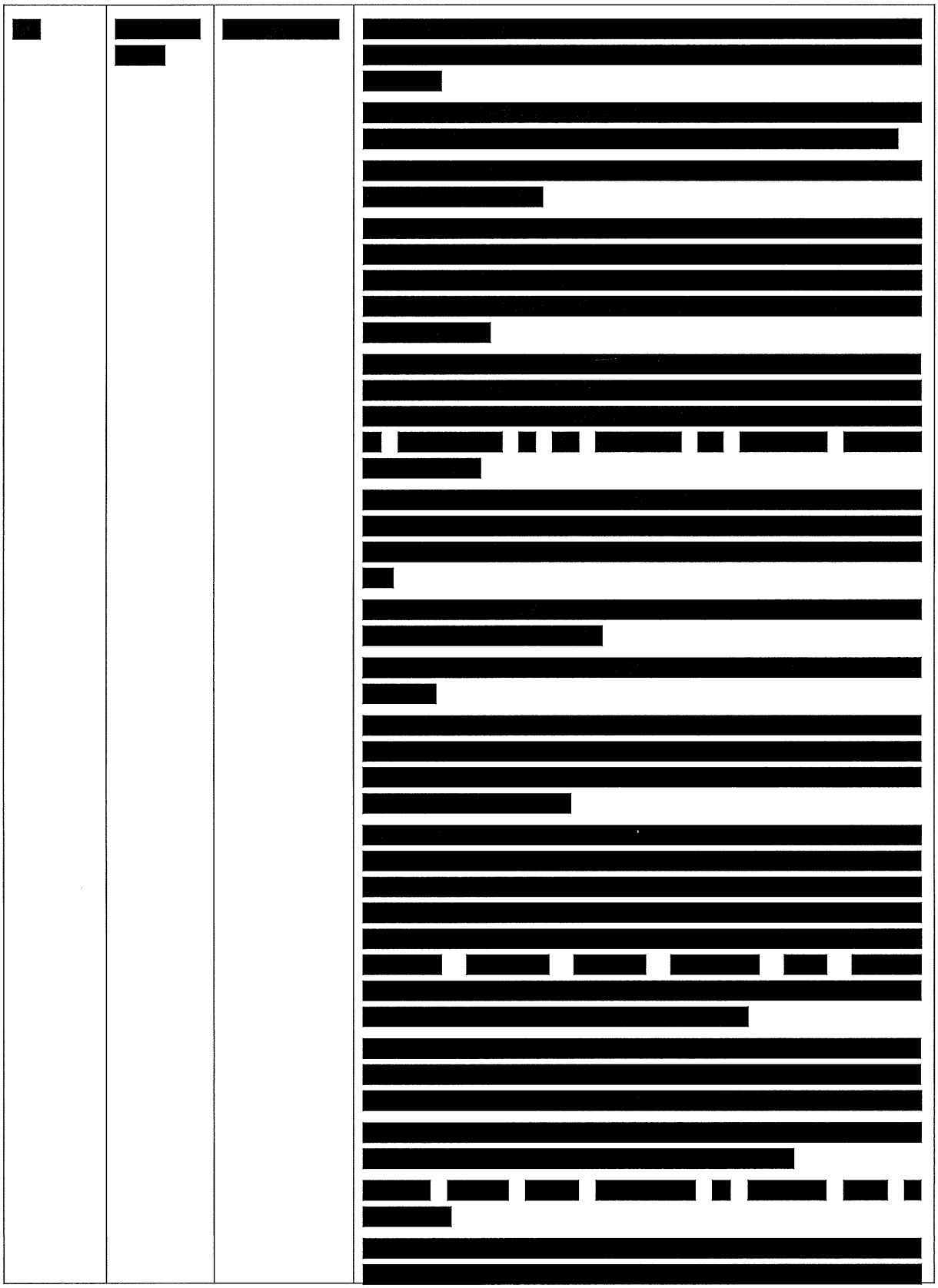

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LIST OF ABBREVIATIONS

Abbreviation	Full Term
ADI	Actual Dose Intensity
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
$AUC_{(0-24)}$	Area Under the Plasma Concentration-Time Curve from 0 to 24 Hours
$AUC_{(0-t)}$	Area Under the Plasma Concentration-Time Curve from 0 to the Time of the Last Measurable Concentration
AUC_{ss}	Area Under the Plasma Concentration-Time Curve from 0 to the End of Dosing Interval
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BOR	Best Overall Response
CI	Confidence Interval
CL_{ss}/F	Apparent Plasma Clearance at Steady State
C_{max}	Maximum Plasma Concentration
CM	Concomitant Medication
CR	Complete Response
CRF	Case Report Form
CRR	Complete Response Rate
CSP	Clinical Study Protocol
CSR	Clinical Study Report
$C_{ss\ max}$	Maximum Plasma Concentration at Steady State
$C_{ss\ min}$	Minimum Plasma Concentration at Steady State
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DoR	Duration of Response
DLCO	Diffusing Capacity of Lung for Carbon Monoxide
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
EDC	Electronic Data Capture

Abbreviation	Full Term
FEV1	Forced Expiratory Volume in 1 Second
FEV1PP	Percent Predicted FEV1
FVC	Forced Vital Capacity
ICH	International Council for Harmonisation
INR	International Normalized Ratio
IRC	Independent Review Committee
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multi-gated Acquisition Scan
NC	Not Calculable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NQ	Not Quantifiable
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PFT	Pulmonary Function Test
PK	Pharmacokinetics
PKS	Pharmacokinetics Set
PT	Preferred Term
PTCL	Peripheral T-cell lymphoma
QD	Once Daily
QTcF	Fridericia Corrected QT
RDI	Relative Dose Intensity
r/r PTCL	Relapsed or Refractory Peripheral T-cell Lymphoma
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SD	Stable Disease

Abbreviation	Full Term
SOC	System Organ Class
SPD	Sum of the Product of the Perpendicular Diameters
TEAE	Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Event
TLG	Table, Listing and Graph
T_{max}	Time to C_{max}
$T_{ss\ max}$	Time to $C_{ss\ max}$
TTR	Time to Response
ULN	Upper Limit of Normal

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the analyses required for Part B of study DZ2019J0005, which is a phase 2, open-label, single-arm, pivotal study of AZD4205 treating patients with relapsed or refractory peripheral T-cell lymphoma (r/r PTCL). The statistical analyses required for part A of DZ2019J0005 (phase 1) were documented in a separate analysis plan.

The SAP contains a more technical and detailed elaboration of the analysis described in the Clinical Study Protocol (CSP). It also includes detailed procedures for executing the statistical analysis required.

The SAP was written based on the following documents:

Document	Version #	Date
CSP	5.0	November 25, 2020
Case Report Form (CRF)	3.0	January 28, 2021
Independent Review Charter	2.0	July 02, 2021

2. OVERVIEW AND INVESTIGATIONAL PLAN

2.1 Study Objectives and Endpoints/Estimand

The objectives of Part B of study DZ2019J0005 are listed below.

2.1.1 Primary Objective, Endpoint and Estimand

Primary Objective	Endpoint/Variable
• To assess the anti-tumor efficacy of AZD4205 using CT-based objective response rate (ORR) as primary efficacy endpoint in patients with r/r PTCL	• CT-based ORR evaluated by independent review committee (IRC), according to 2014 Lugano classification

Estimand of primary objective

Treatment: Participants will receive AZD4205 capsule.

Population: Patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). Evaluable for CT-based response set will be used for analysis, including all dosed central pathology confirmed PTCL participants with baseline measurable disease confirmed by IRC using CT imaging.

Variable (or endpoint): Binary variable indicating whether a participant is a responder who achieved complete response (CR) or partial response (PR), evaluated by IRC based on CT imaging according to Lugano criteria.

Intercurrent Events and strategies:

Intercurrent Events	**Strategies for ORR**
Discontinuation of study treatment due to reasons other than progressive disease (PD)	Treatment policy: Occurrence of intercurrent event ignored.
PD	While on treatment: The intercurrent event is already captured in the variable definition.
New anti-cancer therapy	While on treatment: Response to treatment prior to the occurrence of the intercurrent event is of interest.

Population-level summary: CT-based ORR assessed by IRC according to Lugano.

2.1.2 Secondary and Other Objectives, Endpoints

Secondary and other Objectives	**Endpoints/Variables**
• To assess the anti-tumor efficacy of AZD4205 using other CT-based efficacy endpoints in patients with r/r PTCL	• Duration of response (DoR), complete response rate (CRR), progression free survival (PFS), and time to response (TTR) assessed by IRC based on CT imaging, according to 2014 Lugano classification • Investigators-assessed efficacy endpoints based on CT imaging per Lugano criteria, such as ORR, DoR, CRR, PFS, TTR
• To assess the safety and tolerability of AZD4205 in patients with r/r PTCL	• Adverse events (graded by CTCAE version 5.0)
• To characterize the PK of AZD4205 in plasma	• PK parameters derived from plasma concentrations of AZD4205
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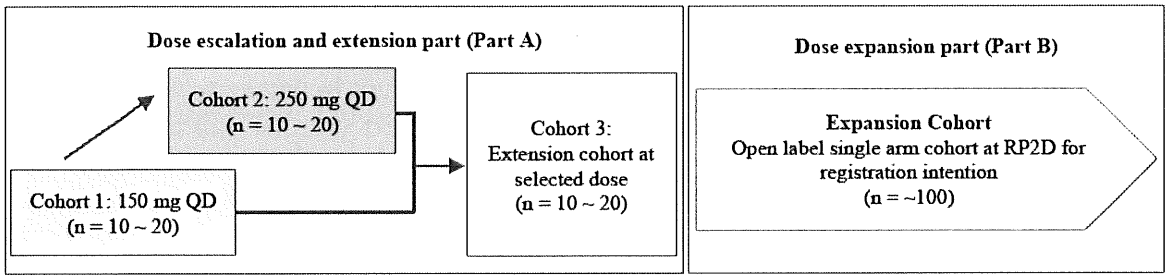
2.2 Overall Study Design

This is a phase I/II, open-label, multicenter study of AZD4205 administered orally in patients with r/r PTCL to determine its safety, tolerability, PK, and anti-tumor activity. The study design allows an escalation of dose with intensive safety monitoring to ensure the safety of the participants. The overall study includes Part A and Part B, and this SAP focuses on Part B only.

Figure 1 Study Flow Chart



Footnote: Eligible patients must have pathologically diagnosed PTCL, and have relapsed from or been refractory/intolerant to SoC
QD: once daily (dose frequency)

Part B of the study is designed as an open-label single arm cohort, which is planned to enroll around 100 participants with PTCL who have relapsed after or been refractory/intolerant to ≥ 1 (but not > 3) prior treatment regimen(s). The primary objective of this part is to evaluate anti-tumor efficacy of AZD4205 at recommended phase II dose (CT-based ORR assessed by IRC per Lugano criteria as primary endpoint) in patients with r/r PTCL. This part will also assess the safety, tolerability, PK, and anti-tumor efficacy (other endpoints) of AZD4205 at recommended phase II dose. Results of this part are planned to be used for marketing application of AZD4205 in patients with r/r PTCL.

This part of the study is composed of an initial screening phase, a single-arm treatment phase, a follow-up phase and a survival phase:

- Screening phase: Screening evaluations will be performed within 28 days prior to the first dose of study drug. Participants will sign the informed consent form prior to any screening evaluations. Please refer to Appendix A for details on screening procedures.

- Treatment phase: All participants will be treated with AZD4205 at 150 mg once daily, administered orally and will continue to be treated until disease progression, unacceptable toxicity, death, withdrawal of consent, or the study is terminated by the sponsor. A treatment cycle consists of 21 days. During treatment, CT scans of the same sites as screening will be done for tumor response assessment within 7 days of Day 1 of Cycle 3, 6, 9 and then every 3 cycles until PD or withdrawal from the study.

- Follow-up phase: A follow-up should be made after 28 days (± 7 days) following the last dose of the study treatment for safety follow-up.

- Survival phase: Participants will be followed up for survival via phone contact (with participant's guardian, if applicable) every 3 months after the participant's last visit until

withdrawal of consent, lost to follow-up, death, or the date of data cut-off for the final analysis.

2.3 Randomization

Not applicable.

2.4 Determination of Sample Size

For Part B dose expansion cohort, the assumption of IRC based ORR is 27%. With a sample size of 100 participants will have 84.5% power to reject the null hypothesis of ORR = 15% at 2-sided 5% significant level with binomial exact test. We referred to the null hypothesis in the pivotal study design of pralatrexate (O'Connor OA et al. 2011) and chidamide (Shi Y et al. 2015). With an observed ORR of 27% (27/100), the 95% exact CI is (18.6%, 36.8%).

3. ANALYSIS SET

3.1 All Participants

All participants screened (who signed informed consent form) will be included in this analysis set. It's mainly used for the individual data listing, and the overall summary of screen failures.

3.2 Safety Analysis Set

All participants treated with at least one dose of AZD4205 (all treated participants) will be included in the safety analysis set.

Safety analysis set is the primary analysis set for safety data, demographic data, exposure data.

3.3 Evaluable for CT-based Response Set

All dosed and central pathology confirmed PTCL participants with baseline measurable disease using CT imaging will be included in the evaluable for CT-based response set.

[redacted]

3.6 Evaluable for Survival Set

The evaluable for survival set will include all dosed and central pathology confirmed PTCL participants. This analysis set is mainly used for PFS [redacted] analysis.

3.7 Pharmacokinetics Set (PKS)

The pharmacokinetics set will include all dosed participants with at least one reportable AZD4205 plasma concentrations and no important adverse events or protocol deviations that may impact PK. The statistical analysis of PK data will be performed based on the PKS.

4. ENDPOINTS DEFINITION AND DERIVATION

4.1 Efficacy Endpoints

The efficacy endpoints based on the tumor assessments will be assessed according to the Lugano Classification for non-Hodgkin lymphoma (see Session 6.9 and Appendix VI of the CSP for details). The overall response for each participant may be provided from sources as illustrated below:

- For IRC-assessed efficacy endpoints: Final IRC-reported participant level overall response including Best Response, Date of Progression (if applicable), and Date of First Response (if applicable)
- For investigators-assessed efficacy endpoints: Investigator (local radiology) overall responses at each assessment/time point. Participant overall response date will be derived by program (see details in Section 4.1.2.5).

4.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is ORR, defined as the proportion of achieving either a PR or CR, which is assessed by IRC based on CT imaging, according to the Lugano Classification for non-Hodgkin lymphoma. Best overall response (BOR) (which contributes to the ORR) is defined as the best response recorded from date of first dosing until disease progression/recurrence or taking new anticancer therapy. Participants without post-baseline assessments to determine disease status will be classified as non-responders.

During treatment, CT scans of the same sites as screening will be done for tumor response assessment within 7 days of Day 1 of Cycle 3, 6, 9 and then every 3 cycles until PD or withdrawal from the study. Any other sites at which new disease is suspected should also be appropriately imaged. Any participant who discontinues study treatment for reasons other than disease progression should have response assessment performed as scheduled in the CSP until disease progression, or death occurs, unless consent is withdrawn.

4.1.2 Secondary Efficacy Endpoints

4.1.2.1 DoR assessed by IRC based on CT

DoR will be derived from those participants who had a CR or PR only.

DoR assessed by IRC based on CT is defined as the time from the date of first documented response until the date of documented progression or death due to any cause. Documented response and progression are both identified based on CT imaging evaluated by IRC. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the first visit response of PR or CR. If a participant does not progress following a response, then his/her duration of response will use the PFS censoring time.

The algorithm for DoR is provided below:

DoR (months) = (date of event/censoring – date of first response+1)/30.4375.

4.1.2.2 CRR assessed by IRC based on CT

CRR assessed by IRC based on CT is defined as the proportion of achieving CR, which is assessed by IRC based on CT imaging, according to the Lugano Classification for non-Hodgkin lymphoma.

4.1.2.3 PFS assessed by IRC based on CT

PFS is defined as the time from the date of first dosing until the date of objective disease progression as defined by Lugano classification or death (by any cause) regardless of whether the participant discontinues the study treatments. Progression is identified based on CT imaging evaluated by IRC. Participants who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable tumor response assessment. More censoring rules for PFS are presented in Table 1. Symptomatic deterioration will not be regarded as a progression event.

The PFS will be calculated as:

PFS (months) = (date of event/censoring –first dose date of AZD4205+1)/30.4375.

Table 1 Censoring Scheme for PFS

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline or any post-baseline tumor assessments and without death within two visits (112 days from date of first dose)	Date of first dose	Censored

No.	Situation	Date of Progression or Censoring	Outcome
2	No baseline or any post-baseline tumor assessments and died within two visits (112 days from date of first dose)	Date of death	Event
3	Progression documented between scheduled visits	Date of first radiological PD	Event
4	No progression at the time of data cut-off/discontinuation from the study	Date of last visit with *adequate radiological tumor assessment prior to data cut-off or discontinuation from the study.	Censored
5	Treatment discontinuation for reason other than radiological PD	Data after discontinuation of treatment will be included when determining the time to progression	Event / Censored
6	New anticancer treatment started	Date of last adequate radiological tumor assessment with documented non-progression before start of new treatment	Censored
7	Death before first PD assessment	Date of death	Event
8	Death between scheduled tumor assessment visits	Date of death	Event
9	Death or progression after more than one missed visit (CT scans will be done for tumor assessments within 7 days of Day 1 of Cycle 3, 6, 9 and then every 3 cycles thereafter until PD)	Date of last adequate radiological tumor assessment with documented non-progression	Censored

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

4.1.2.4 TTR assessed by IRC based on CT

TTR will be derived from those participants who had a CR or PR only.

TTR assessed by IRC based on CT is defined as the time from the date of first dosing to the time of the initial response of PR or CR. Response is identified based on CT imaging evaluated by IRC.

The algorithm for TTR is provided below:

TTR (months) = (date of first response – first dose date of AZD4205 + 1)/30.4375.

4.1.2.5 Endpoints assessed by Investigators based on CT

In addition to the primary and secondary efficacy endpoints described above, the same set of endpoints (ORR, DoR, CRR, PFS and TTR) assessed by investigators based on CT imaging will also be regarded as secondary endpoints.

For Investigators based endpoints, the date of assessment will be derived following similar rule as in Independent Review Charter session 10.1.

If an assessment may include several methods of evaluation performed over a period of several days within a window of time around an expected assessment date, the date of assessment will be recorded as the date of the last radiographic included in the series for that assessment.

The CT date of progression is defined as the radiographic assessment date of the first time point with overall response as PD for that assessment.

The CT date of first response is defined as the radiographic assessment date when the criteria for CR or PR were first met.

4.2 Pharmacokinetics

4.2.1 Drug Concentration

In Part B dose expansion cohort, about 20% of the total participants at the selected sites will be invited for intense PK study on Cycle 1 Day 1 and Cycle 2 Day 1. The remaining participants will be invited for sparse PK study on Cycle 1 Day 1 and Cycle 2 Day 1.

Venous blood samples (2 mL) per visit in time windows will be taken at the times presented in Table 2 and Table 3 for determination of AZD4205 in plasma. A 5 min window will be allowed for samples taken at 1 h; a 10 min window for samples taken at 2-8 h; a 15 min window for samples taken at pre-dose; a 1 h window for samples taken at 24 h.

Table 2 PK Blood Samples Schedule for Intense PK Study (Part B)

Time relative to dose	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 4 Day 1	Cycle 6 Day 1
Pre-dose	×	×	×	×	×
1 hours	×		×		
2 hours	×		×		
4 hours	×		×		
6 hours	×		×		
8 hours	×		×		
24 hours*	×		×		

Footnote: The PK sampling at 24 hours post dosing should be taken before the next dose.

Table 3 PK Blood Sampling Schedule for Sparse PK Study (Part B)

Time relative to dose	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 4 Day 1	Cycle 6 Day 1
Pre-dose	×	×	×	×	×
4 hours			×		

If a participant misses any doses of AZD4205 within 3 days of PK sampling, the Clinical Pharmacologist will assess any effect and suggest the changes required on the timing of the PK assessments.

4.2.2 Pharmacokinetic Parameters

The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard non-compartmental methods. Where possible the following PK parameters will be determined for AZD4205.

Following the first dose of the study on day 1:

Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve from zero to 24 hours ($AUC_{(0-24)}$), from zero to the time of the last measurable concentration ($AUC_{(0-t)}$).

Following the multiple dose part of the study:

Maximum plasma concentration at steady state ($C_{ss\ max}$), time to $C_{ss\ max}$ ($t_{ss\ max}$), minimum plasma concentration at steady state ($C_{ss\ min}$), area under the plasma concentration-time curve from zero to the end of the dosing interval (AUC_{ss}), extent of accumulation on multiple dosing (RAC) for AUC and C_{max}, and apparent plasma clearance at steady state (CL_{ss}/F) will be determined where possible.

The C_{max}, $C_{ss\ max}$, t_{max} and $t_{ss\ max}$ will be determined by inspection of the concentration-time profiles. The $AUC_{(0-t)}$, $AUC_{(0-24)}$ and AUC_{ss} will be calculated using the linear up/log down rule. The RAC will be calculated as the ratio of the AUC $_{(0-24)}$ (or C_{max}) on Cycle 2 Day 1 and Cycle 1 Day 1. CL_{ss}/F will be determined from the ratio of dose/AUC_{ss}.

4.3 Safety

4.3.1 Extent of Exposure

Extent of exposure will be checked for AZD4205.

Total duration of exposure (months) will be calculated as:

(date of last dose – date of first dose + 1)/ 30.4375

For participants who are still undergoing study treatment at the time of analysis, date of last dose will be the cut-off date for the analysis, and the dose will be the planned dose, if dose date and amount weren't recorded in EDC.

If the first/last dose date is missing/partial, the duration can't be calculated.

Cumulative dose will be calculated as sum of the doses (mg) taken during the treatment period. Actual Dose Intensity (ADI) is the total amount of drug given in a fixed unit of time. The Relative Dose Intensity (RDI) is the ratio of actual dose intensity to the planned dose intensity and can be expressed as a percentage.

Actual Dose intensity (mg/day) = cumulative dose (mg)/total duration of exposure (day).

Relative dose intensity (%) = actual dose intensity/planned dose intensity*100%, where planned dose intensity (mg/day) is the initial dose per day planned in the CSP.

4.3.2 Adverse Events (AE)

All AEs recorded on the CRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 22.0 (or a later version if updated during the study).

The AEs will be classified as pre-treat AEs or treatment-emergent AEs (TEAEs), as below:

- Pre-treat AEs are events that start prior to the date of the first dose of investigational product.
- TEAEs are events with start or worsen on or after the date of first dose of treatment and up to 28 days after last dose of treatment or the day prior to the subsequent anti-cancer therapy initiation after treatment discontinuation (including participation in a new clinical trial), whichever is earlier.

Assessment of AE grade will be based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 5.0).

A treatment-related AE is an AE considered by the investigator as 'related' or with unknown/missing relationship to treatment.

4.3.3 Laboratory Data

Data for the hematology, serum chemistry, coagulation and urinalysis analytes will be collected as scheduled in the CSP, through local laboratory.

Serum Chemistry	**Hematology**	**Coagulation**	**Urinalysis**
Albumin	Hemoglobin	PT	U-Glucose
Alkaline phosphatase	Hematocrit	PTT or aPTT	U-Protein
ALT	Platelet count	INR	U-Blood**
AST	Red blood cell count		U-Leucocytes***
Bicarbonate	White blood cell count		
Blood urea nitrogen	Differential cell count:		
Calcium	• Basophils		
Chloride	• Eosinophils		
Creatinine	• Lymphocytes (absolute)		
CRP	• Monocytes		
Glucose	• Neutrophils (absolute)		
LDH	Reticulocytes		
NT-pro BNP			
Phosphate			
Potassium			
Sodium			
Total bilirubin			
Total serum protein			
Troponin T* or Troponin I			
Total cholesterol			
Triglyceride			
HDL-C			
LDL-C			

Apo-A			
Apo-B			
Creatine Kinase			

aPTT = activated partial thromboplastin time; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; PTT = partial thromboplastin time. *High sensitivity cTnT (hs-cTnT) assay (if applicable) is recommended. ** In case of positive urine blood test, assessment of red blood cell count in urine should be performed. *** In case of positive urine leucocytes test, assessment of leucocytes count in urine should be performed.

All laboratory data will be converted to International System of Units (SI) for analysis purpose. All values will be checked against the reference range (if available) and values out of reference range will be flagged as high or low (or abnormal for urinalysis data).

The CTCAE grade will be assigned for the laboratory tests applicable, following the criteria in NCI-CTCAE version 5.0. The detailed criteria are shown in Appendix B. Data not meeting the existing criteria will be assigned as grade 0. Baseline grade will also be assigned as 0 for those tests whose CTCAE criteria do not apply to baseline data (e.g., AST, ALT, ALP, and total bilirubin).

To examine post-baseline laboratory abnormalities associated with liver function, participants meeting the criteria in Appendix C will be identified for further analysis.

Creatinine Clearance

Estimated creatinine clearance will be calculated using the Cockcroft and Gault formula as below:

Men: [(140 – age) × weight (kg) × 1.23] / creatinine (μmol/L)

Women: [(140 – age) × weight (kg) × 1.04] / creatinine (μmol/L)

4.3.4 Electrocardiograms (ECG)

Twelve-lead triplicate ECG will be performed following the schedule in the CSP, and is shown in Appendix A. The following quantitative ECG measurements will be taken:

- Heart rate (bpm)
- PR interval (msec)
- RR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- Fridericia Corrected QT (QTcF) interval (msec)

If multiple measurements exist at the same visit/schedule time point, average of the quantitative measurement will be used for analysis.

4.3.5 Vital Signs

The following vital signs will be collected following the schedule in the CSP.

- Systolic and diastolic blood pressure (mmHg)
- Height (cm)
- Weight (kg)
- Pulse rate (bpm)
- Body temperature (°C)

The CTCAE grade will be assigned for blood pressure following the criteria in NCI-CTCAE version 5.0. The detailed criteria are shown in Appendix B. Data not meeting the existing criteria will be assigned as grade 0.

4.3.6 Physical Examination and ECOG

Physical examination and Eastern Co-operative Oncology Group (ECOG) will be performed following the schedule in the CSP and are shown in Appendix A.

4.3.7 Echocardiogram/MUGA Scan

Echocardiogram or multi-gated acquisition scan (MUGA) scan to assess Left Ventricular Ejection Fraction (LVEF (%)) will be conducted following the schedule in the CSP and shown in Appendix A. Additional Echocardiogram or MUGA scan will be performed whenever necessary as clinically indicated throughout the study.

4.3.8 Pulmonary Function Tests (PFTs)

PFTs will be performed following the schedule in the CSP. The following tests will be taken.

- FVC (L)
- FEV1 (L)
- FEV1/FVC ratio (%)
- FVC (percent predicted) (%)
- FEV1 (percent predicted) (FEV1PP) (%)
- DLCO (mmol/min/kPa)

- DLCO (mL/min/mmHg)

5. STATISTICAL METHODS

5.1 General Principles

All data processing, summarization and analyses will be performed using SAS® 9.4 (or higher) in Dizal data warehouse.

The data from different parts of study will be analyzed and reported separately, unless otherwise specified.

Unless otherwise specified, the typical descriptive statistics for continuous variables will include number of participants (n), mean, standard deviation, median, minimum (min), and maximum (max) values. Categorical variables will be summarized by presenting the number and percentage of participants in each category.

The clinical cut-off date for the primary analyses is expected to occur at least 6 months after the last initial tumor response assessed by IRC.

5.2 Participant Disposition and Analysis Sets

Participant disposition will be summarized in the safety analysis set and evaluable for CT-based response set separately and will include the number and percentage of participants:

- Treatment status (ongoing, discontinued)
- Study status
- Survival status at the last contact (alive, dead, unknown, lost to follow-up)
- Time on study (months), calculated as (date of study completion/discontinuation - first dose date of AZD4205+1)/30.4375. For participants who are still on study at the time of analysis, the data cut-off date will be used in the calculation.

In addition, for the participants who discontinued the treatment or who discontinued from the study, a breakdown of the primary reasons will be presented.

The number and percentage of participants included in each analysis set (safety analysis set, evaluable for CT-based response set, [redacted], evaluable for survival set, pharmacokinetics set) will also be reported based on safety analysis set.

The number of participants screened but not enrolled as well as a summary of the reasons for screen failure will be produced, based on all participants. No other information for screen failures will be presented.

The participant disposition data for all participants will be listed in the individual data listing. The treated participants excluded from evaluable for CT-based response set and PK analysis set will also be listed.

5.3 Protocol Deviation

The number and percentage of participants with major protocol deviations will be summarized by category and will be listed in the safety analysis set.

5.4 Demographic and Other Baseline Characteristics

5.4.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized in the safety analysis set and evaluable for CT-based response set, respectively. Standard descriptive statistics will be presented for the continuous variables below:

- Age (years)
- Height (cm) at baseline
- Weight (kg) at baseline
- Body mass index (BMI) in kg/m^2, calculated as ($weight/height^2$) where weight is in kg and height is in m

The number and percentage of participants will be presented for the categorical variables below:

- Age group (<65 years, ≥65 years)
- Sex
- Race
- Ethnicity
- Country
- Geographical region (Asia: China and S. Korea, Non-Asia: United States and Australia)
- ECOG performance status at baseline (0, 1, 2)
- Bone marrow involvement at baseline by histology (yes, no)
- FDG-avid disease (yes, no) (only for participants with baseline PET scan)
- LDH elevation at baseline (yes, no)

No formal tests of statistical significance will be performed on the demographic and baseline data.

5.4.2 Medical History and Surgical History

Medical history will be coded using the MedDRA version 22.0 (or a later version if updated during the study).

All medical history will be summarized in the safety analysis set. Number and percentage of participants with any medical history will be reported, together with the number of participants with at least one medical history within each MedDRA system organ class (SOC) and preferred term (PT).

All the medical history and surgical history reported will be listed in the individual data listing.

5.4.3 Pathology

The number and percentage of participants in histology subtype will be reported for both central lab and local lab, using the safety analysis set and evaluable for CT-based response set respectively. Tumor location at initial diagnosis, Ann Arbor symptoms upon the entry of study, revised Ann Arbor staging upon the entry of the study and time from initial diagnosis (months) will also be summarized.

Pathology will be presented in data listing.

5.4.4 Prior Cancer Therapy

Prior cancer therapy will be summarized by therapy class, agent (decoded by Anatomical Therapeutic Class (ATC) level 2 and preferred name) for the safety analysis set. Participants will be counted only once for each therapy class if they have multiple records of the same ATC level in the database. Participant who had prior stem cell transplantation in surgical history, the number of prior treatment lines, BOR of the last prior line of therapy will be summarized as baseline check.

The number (%) of participants who had received the following anti-cancer therapies will be summarized.

- Chemotherapy as well as the subcategory of Pralatrexate and Mitoxantrone liposome
- Histone deacetylase inhibitors as well as the subcategory of Chidamide and Belinostat
- CD30 target treatment
- ALK inhibitor

Radiotherapy (prior, concomitant and post IP discontinuation) and cancer therapy (prior and after end of study treatment) will be presented in data listings.

5.4.5 Prior and Concomitant Medication and Therapies

Prior and concomitant medications received by participants will be coded using the World Health Organization Drug Dictionary version Global B3 Mar 2019 (or a later version if updated during the study), Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

Prior medications are those with a stop date prior to the first dose date of investigational product, or medications with a start date prior to the first dose date of investigation product and a stop date after the first dose date of investigation product.

Concomitant medications are those administrated during the period from the first dose date of investigational product, till 28 days after the last dose date. i.e., the medications with a start date on or after the first dose date of the investigational product and no later than 28 days after the last dose date; or those with a start date before the first dose date of the investigational product and a stop date on or after the first dose date of the investigational product or ongoing at the end of study.

If a medication cannot be classified as prior or concomitant after applying imputation rules (Section 7.2) for missing/incomplete dates, it will be classified as concomitant.

Prior medications and concomitant medications will be summarized separately in safety analysis set. The number and percentage of participants using any medication will be displayed together with the number and percentage of participants using at least one medication within each therapeutic class (ATC-Level 2) and preferred name.

Prior medications and concomitant medications will be listed together in the individual data listing, with the flags for prior or concomitant medication.

5.4.6 Extent of Exposure

The extent of exposure data will be listed and summarized in safety analysis set and evaluable for CT-based response set respectively.

Total duration of exposure, cumulative dose, ADI, RDI will be summarized by the following: mean, standard deviation, minimum, maximum, median and number of observations. Total duration of exposure (<3, ≥3 - <6, ≥6 - <9, ≥9 - <12, ≥12 months, etc.) and RDI (<80%, 80-100%, >100%) will also be summarized as categorical variable with number and percentage of participants in each category presented. In addition, the number and percentage of participants with at least one dose interruption and at least one dose reduction will be presented. For participants with dose interruption due to AE, the longest duration in days with dose interruption will be summarized.

5.5 Efficacy

5.5.1 Primary Efficacy Analysis

The primary endpoint for Part B of this study is ORR defined as the proportion of achieving either a PR or CR, which is assessed by IRC based on CT imaging, according to the Lugano Classification for non-Hodgkin lymphoma.

The analysis of primary endpoint will be performed in evaluable for CT-based response set. ORR will be analysed using the exact binomial test for single proportion at two-sided significance level of 5%.

The Clopper-Pearson 95% confidence interval (CI) of ORR will also be provided.

The number (%) of participants with best objective response will also be provided in the following categories: CR, PR, SD, PD and Non-Evaluable (NE).

5.5.2 Secondary Efficacy Analysis

Efficacy endpoints related to Lugano classification will be analysed and reported based on CT imaging evaluated by IRC and investigators respectively, using the same statistical analysis method. The analysis methods for DoR, PFS, TTR and change in tumor size are described below regardless of assessment by IRC or investigators.

5.5.2.1 DoR

The definition and derivation of DoR can be found in Section 4.1.2.1.

The analysis population for DoR will be the subset of the evaluable CT-based response set with a best overall response of CR/PR.

Number of participants achieving a best objective response of CR/PR, the number (%) of responders with event or censored will be presented. The duration of response rates at specific time points and quartiles (25%, 50%, 75%) of DoR will be provided with 95% CIs based on the Kaplan-Meier method, along with a Kaplan Meier plot.

To demonstrate tumor response episodes over the treatment period, swimmer plot of tumor response overtime will be provided based on participants in evaluable CT-based response set.

5.5.2.2 PFS

The definition and derivation of PFS can be found in Section 4.1.2.3.

The analysis population for PFS will be the evaluable for survival set. The number (%) of participants with event or censored before data cut-off will be reported. Breakdown of events (PD or death) and censors will also be summarized.

The progression-free survival rates at specific time points and quartiles of PFS will be estimated based on Kaplan-Meier method. PFS data will also be displayed graphically using a Kaplan-Meier plot.

5.5.2.3 TTR

The definition and derivation of TTR can be found in Section 4.1.2.4.

The analysis population for TTR will be the subset of the evaluable CT-based response set with a best overall response of CR/PR.

A Kaplan Meier plot, time to response rates at specific time points, quartiles of TTR and 95% CI (calculated from the Kaplan-Meier) will be presented.

5.5.2.4 Change in tumor size

The analysis population for change in tumor size will be the evaluable CT-based response set. Participants without observed post-baseline target lesion measurements for the visit of interest will be excluded.

The absolute values and percentage change in target lesion tumor size from baseline will be summarized using descriptive statistics and presented by time point. Best change will also be summarized. Tumor size will also be presented graphically using waterfall plots, presenting each participant's percentage of best change in tumor size as a separate bar.

5.5.2.5 ORR assessed by investigators based on CT

ORR assessed by investigators based on CT will be analysed using the same method described in Section 5.5.1, except for exact binomial test.

5.5.3 Sensitivity Analysis

No sensitivity analysis will be conducted.

5.5.4 Subgroup Analyses

Subgroup analyses will be performed for IRC-assessed CT-based tumor response (ORR) for evaluable for CT-based response set provided that there is adequate sample size in the respective groups. If the number of participants is small in a specific level of the subgroup variables, appropriate combination of the levels will be considered for subgroup analyses. If data is appropriate, the following subgroup variables will be used, other subgroup variables may also be used.

- Histology subtype by central pathology review
- Country (China, non-China)

- Geographical region (Asia: China and S. Korea, Non-Asia: United States and Australia)
- Age group (< 65 years, ≥ 65 years)
- Sex (male, female)
- Prior line(s) of anti-cancer therapy (<2, ≥2)
- Prior Chidamide treatment (Yes, No)
- Bone marrow involvement at baseline by histology (Yes, No)
- ECOG performance status at baseline (0, ≥1)

Subgroup analyses will be displayed graphically using a forest plot.

[redacted]

[redacted]

5.6 Pharmacokinetics

5.6.1 Summary of Drug Concentration

Drug concentration data will be analysed and reported in PKS.

Concentrations of AZD4205 in plasma following single dose and multiple doses will be summarized separately by nominal time point and sampling category (intense only, sparse combining intense). Extra measurements (such as unscheduled or repeat assessments) will not be included in the summary tables but will be included in individual data listings.

The following summary statistics will be provided for concentration in the summary tables:

- Number of observations
- Number of observations below Lower Limit of Quantification (LLOQ)
- Arithmetic mean calculated using untransformed data
- Standard Deviation (SD) calculated using untransformed data
- The geometric mean (G_{mean}, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- Geometric coefficient of variation (CV, calculated as $100\sqrt{\exp(s^2) - 1}$, where s is the standard deviation of the data on a log scale)
- Geometric mean ± SD (calculated as exp[μ±s])

- Minimum
- Median
- Maximum

The drug concentration will also be displayed graphically. Plasma concentration will be plotted (on the linear and semi log-scale) versus time for each individual participant. The geometric mean will also be plotted versus the nominal time point. And the error bar for geometric mean + SD will be added if appropriate.

All drug concentration data collected will be presented in the individual data listing, including the data for participants excluded from PKS and the extra measurements (such as unscheduled or repeat assessments), data of specific time points which are excluded will be flagged with a note.

5.6.1.1 Reporting Concentration below LLOQ

Plasma concentrations that are below the limit of quantification (BLQ) prior to administration of the first dose and up to the first measurable concentration will be counted as zero. Any other time points are excluded from the analysis.

If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantifiable values are excluded from the PK analysis unless there is a scientific rationale not to do so, this will be documented.

Individual concentrations below the LLOQ of the assay will be reported as NQ (not quantifiable) with the LLOQ defined in the Tables, Listings and Graphs (TLGs), except the values precede the first measurable concentration. For descriptive statistics:

- If, at a given time point, 50% or less of the plasma concentrations are not quantifiable (NQ), the geometric mean, geometric CV, geometric SD, arithmetic mean, SD and median will be calculated by substituting the LLOQ for values which are NQ.
- If more than 50%, but not all, of the concentrations are NQ, the geometric mean, geometric CV, geometric SD, arithmetic mean and SD will be reported as not calculable (NC). The max value will be reported from the individual data, and the min and median will be set as NQ.
- If all the concentrations are NQ, the geometric mean and arithmetic mean will be reported as NQ, and the geometric CV, geometric SD and SD will be reported as NC.

The number of values below LLOQ is reported for each time point along with the total number of collected values. Given the first criterion above is met, three observations >LLOQ are required as a minimum for a plasma concentration or PK parameter to be summarised. If only

one or two values above LLOQ are available, data are presented as a minimum and maximum with the other summary statistics as NC.

5.6.2 Summary of Pharmacokinetic Parameters

The derived PK parameters for AZD4205 following single dose and multiple doses will be summarized separately in PKS.

The following summary statistics will be presented for $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}t)}$, AUC_{ss}, C_{max}, $C_{ss\ max}$ and $C_{ss\ min}$:

- G_{mean}, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- CV, calculated as $100\sqrt{\exp(s^2) - 1}$, 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
- Median
- Number of observations

The following summary statistics will be presented for R_{AC} and CL_{ss}/F:

- Arithmetic mean
- Standard deviation
- Minimum
- Maximum
- Median
- Number of observations

The following summary statistics will be presented for t_{max} and $t_{ss\ max}$:

- Median
- Minimum

- Maximum
- Number of observations

All individual PK parameters will be presented in the data listing.

5.7 Safety

5.7.1 Adverse Event

Summary tables of AEs will be produced in safety analysis set. Only the TEAEs will be included in the summaries.

An overview table will be created to present the number and percentage of participants with at least one of the following TEAEs, where participants with more than one TEAE in a particular category will be counted only once in that category.

- TEAE
- TEAE grade 3 or higher
- Treatment-emergent SAE (TESAE)
- TEAE with fatal outcome
- TEAE leading to treatment discontinuation
- TEAE leading to treatment interruption
- TEAE leading to treatment reduction
- Drug-related TEAE
- Drug-related TEAE grade 3 or higher
- Drug-related TESAE
- Drug-related TEAE with fatal outcome
- Drug-related TEAE leading to treatment discontinuation
- Drug-related TEAE leading to treatment interruption
- Drug-related TEAE leading to treatment reduction

The number and percentage of participants reporting each TEAE will be summarized by MedDRA SOC and PT. The following summary tables will be produced:

- TEAEs, by SOC, PT and CTCAE grade (all grades, grade ≥3)
- Drug-related TEAEs, by SOC, PT and CTCAE grade (all grades, grade ≥3)
- TEAEs, by SOC, PT and maximum CTCAE grade
- Drug-related TEAEs, by SOC, PT and maximum CTCAE grade
- TEAEs leading to dose reduction, by SOC and PT
- Drug-related TEAEs leading to dose reduction, by SOC and PT
- TEAEs leading to dose interruption, by SOC and PT
- Drug-related TEAEs leading to dose interruption, by SOC and PT
- TEAEs leading to treatment discontinuation, by SOC and PT
- Drug-related TEAEs leading to treatment discontinuation, by SOC and PT
- TESAEs, by SOC and PT
- Drug-related TESAEs, by SOC and PT
- TEAEs with fatal outcome, by SOC and PT
- Drug-related TEAEs with fatal outcome, by SOC and PT
- Common TEAEs, by SOC, PT and CTCAE grade (all grades, grade ≥3)
- Common drug-related TEAEs, by SOC, PT and CTCAE grade (all grades, grade ≥3)
- Common TEAEs with CTCAE grade ≥3, by SOC and PT
- Common drug-related TEAEs with CTCAE grade ≥3, by SOC and PT
- Common TESAEs, by SOC and PT
- Common drug-related TESAEs, by SOC and PT

In the above summaries, participants with more than one AE within a particular SOC are counted only once for that SOC. Similarly, participants with more than one AE within a particular PT are counted only once for that PT.

For summaries by maximum CTCAE grade, participants with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT.

If CTCAE grade is missing for a TEAE, it will be counted as a missing category in the summary tables by grade.

In all summary tables, the events will be sorted by descending frequency, at SOC and PT level respectively.

The number and percentage of participants in the safety analysis set who died, who died from first dose of study treatment until 28 days after last dose of study treatment, who died more than 28 days after last dose of study treatment as well as the reasons for death will be summarized. All deaths will be listed.

All individual AE data will be listed together, and treatment-emergence status will be flagged in the listing. In addition, corresponding listings of serious AEs (SAEs), AEs leading to dose reduction, dose interruption, treatment discontinuation and AEs resulting in death will be produced. AEs that occurred after participants received subsequent anti-cancer therapy will be flagged in the listing.

Where appropriate, AE subgroup analysis and analysis for adverse event of special interest may be performed.

5.7.2 Laboratory Data

The laboratory tests as specified in 4.3.3 will be summarized in the safety analysis set.

Quantitative laboratory data (except urinalysis) together with change from baseline will be summarized by visit using descriptive statistics, such as mean, standard deviation, median, min and max. By-visit box plots will be provided for selected laboratory tests like ALT, AST, ALP, total bilirubin, creatinine, total cholesterol, triglyceride, potassium, sodium, creatine kinase in serum chemistry, hemoglobin, platelet count, white blood cell count, lymphocytes (absolute), neutrophils (absolute) in hematology, and aPTT, INR in coagulation.

To present the status change in clinical significance from baseline to the worst case (abnormal clinically significant > abnormal not clinically significant > normal) post-baseline, shift tables will be provided for each laboratory test. Only participants with both baseline and post-baseline data non-missing will be included in the shift tables.

For the laboratory tests with applicable CTCAE criteria (details are shown in Appendix B), shift tables will be provided to show the shift from baseline CTCAE grade to the worst grade post-baseline.

The number and percentage of participants with post-baseline CTCAE grade worsened from baseline will also be reported by worsened CTCAE grade (all grades, grade ≥3). For selected laboratory tests, post-baseline CTCAE grade (worst case) compared to baseline will be provided by increase interval (≥1, 1, 2, 3, 4) using the number and percentage of participants.

The number and percentage of participants with post-baseline laboratory abnormalities associated with liver function will be reported according to Appendix C. A quadrant plot of the

maximum post-baseline ALT or AST (X-axis) and the maximum post-baseline total bilirubin (Y-axis) will be provided (vertical line of ALT or AST equal to 3 x upper limit of normal (ULN) and horizontal line of total bilirubin equal to 2 x ULN divide the quadrant plot into four quadrants). The upper right, upper left, and lower right quadrants of the quadrant plot represent the potential Hy's law, cholestasis, and Temple's corollary, respectively. The number and percentage of participants in the three quadrants will be reported separately.

Laboratory data will be included in the individual data listing.

5.7.3 Electrocardiograms

The ECG data will be summarized in the safety analysis set.

The ECG measurements and changes from baseline will be summarized by visit using standard descriptive statistics (mean, standard deviation, median, min and max).

The number and percentage of participants with abnormal ECG measurement (worst case) meeting each criterion below will be reported respectively. Only the post-baseline data will be included for analysis.

- Emerging absolute prolongation in QTcF interval (msec):
  - > 450 and ≤ 480
  - > 480 and ≤ 500
  - > 500
- Change from baseline in QTcF interval (msec):
  - increases from baseline >30 and ≤60
  - increases from baseline >60
- PR interval (msec):
  - >220 msec and increase from baseline >25%
- QRS interval (msec):
  - >120 msec
- Heart rate (bpm):
  - <50 bpm and decrease from baseline >25%
  - >100 bpm and increase from baseline >25%

All the ECG measurements and change from baseline will be listed in the individual data listing, together with the Overall ECG Interpretation.

5.7.4 Vital Signs

Vital signs data together with the changes from baseline will be summarized by visit and time point using standard descriptive statistics (mean, standard deviation, median, min and max) in the safety analysis set.

For the vital sign parameters with applicable CTCAE criteria (details are shown in Appendix B), shift tables will be provided to show the shift from baseline CTCAE grade to the worst grade post-baseline.

5.7.5 Echocardiogram/MUGA Scan

The actual value and change from baseline to each visit will be descriptively summarized (mean, median, standard deviation, min, max) for echocardiogram/MUGA scan by visit in the safety analysis set.

The number and percentage of participants with abnormal LVEF decrease (worst case) meeting each criterion below will be reported respectively. Only the post-baseline data will be included for analysis.

- Absolute value >50%
  - Decrease from baseline ≥ 10% and <20%
  - Decrease from baseline ≥20%
- Absolute value ≥ 40% and ≤50%
  - Decrease from baseline ≥ 10% and <20%
  - Decrease from baseline ≥20%
- Absolute value ≥ 20% and <40%
  - Decrease from baseline ≥ 10% and <20%
  - Decrease from baseline ≥20%
- Absolute value <20%
  - Decrease from baseline ≥ 10% and <20%
  - Decrease from baseline ≥20%

All the LVEF measurements and change from baseline will be listed in the individual data listing.

5.7.6 Pulmonary Function Tests (PFTs)

The actual value and change from baseline to each visit will be descriptively summarized (mean, median, standard deviation, min, max) for PFTs by visit in safety analysis set.

The number and percentage of participants with abnormal FEV1PP and DLCO decrease (worst case) meeting each criterion below will be reported respectively. Only the post-baseline data will be included for analysis.

- FEV1PP
  - ≥70% and ≤99%
  - ≥60% and <70%
  - ≥50% and <60%
  - <50%
- DLCO decrease from baseline
  - ≥ 3 and ≤ 5 (ml/min/mmHg)
  - > 5 and ≤ 8 (ml/min/mmHg)
  - > 8 (ml/min/mmHg)

All the PFTs measurements will be listed in the individual data listing.

5.7.7 Physical Examination and ECOG

Shifts from baseline ECOG scale to post-baseline scale (worst case) will be tabulated in the safety analysis set.

All the ECOG measurements will be listed in the individual data listing.

Abnormal physical examination data will be provided in by-participant listings.

6. INTERIM ANALYSES

No interim analysis will be performed for this study.

7. DATA HANDLING RULES

7.1 Time Points and Visit Windows

Day 1 is defined as the day of first dose of investigational product. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

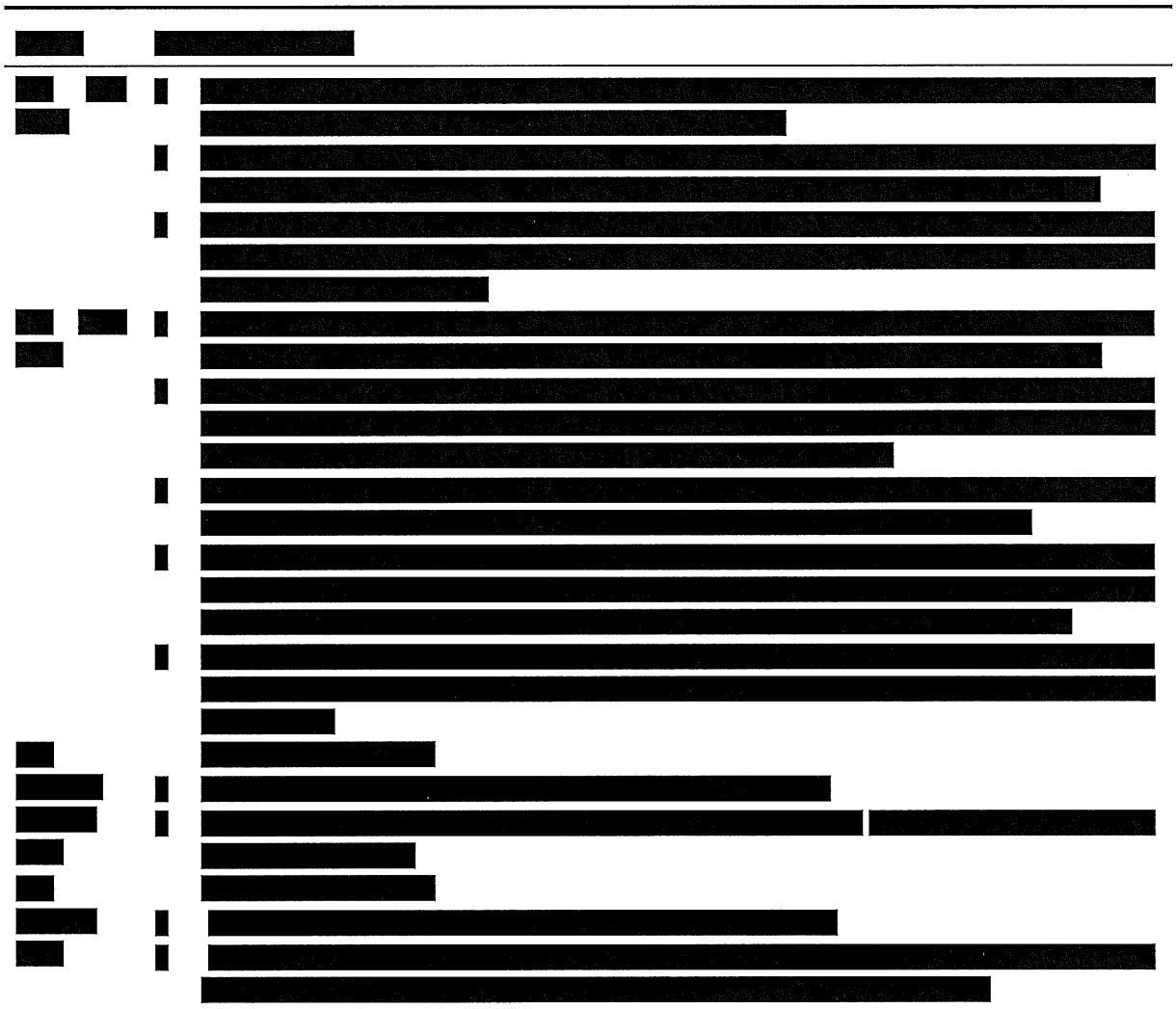
The baseline value is defined as the most recent non-missing value before the first dose of investigational product. The data measured on Day 1 will be considered as candidate of baseline, unless there is information indicating that the data are measured after the dosing.

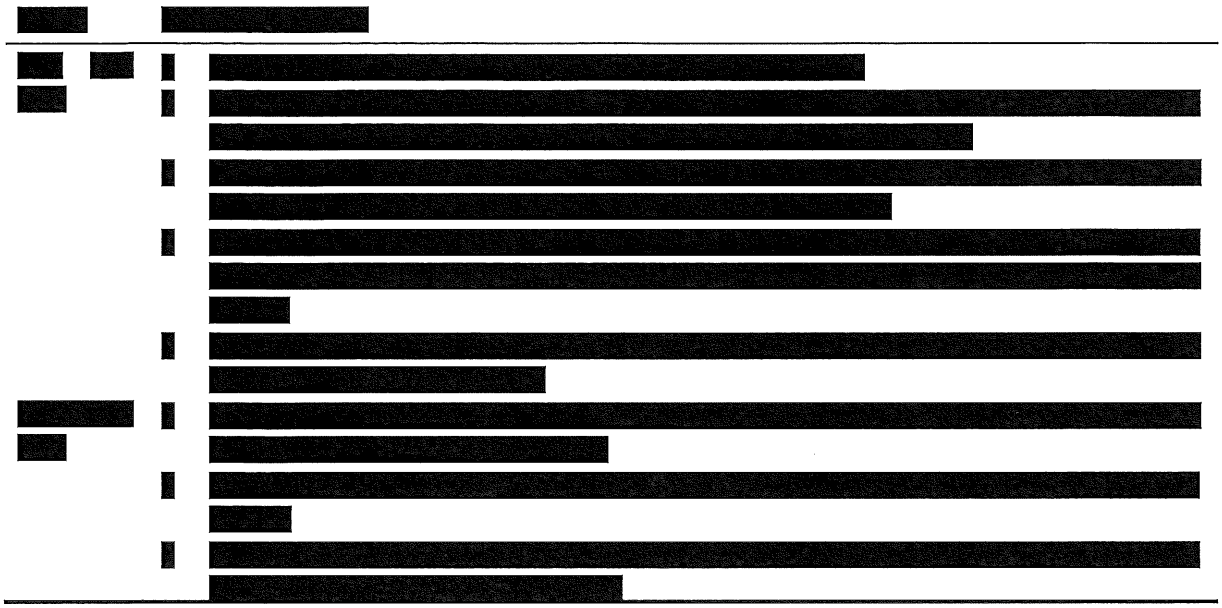
In by-visit summary, all post-baseline data will be analysed using nominal study visits as defined in the Study Schedule and CRF. No visit windows will be applied for summary and analysis and only data from scheduled visits will be included in the summary.

Analysis period is defined as the time from date of first dose to 28 days after last dose or the day prior to the subsequent anti-cancer therapy initiation after treatment discontinuation (including participation in a new clinical trial), whichever is earlier. Analysis period will be used in the safety summaries that require consideration of both scheduled and unscheduled visit data (e.g., summary of post-baseline worse case, etc.).

7.2 Handling of Missing Data and Outliers

The imputation rule for partial/missing dates of AE and prior/concomitant medication (CM) is listed below. End date will be imputed first and start date will be imputed based on the imputed end date. If year of the date is missing, the date will be considered as totally missing and imputed accordingly.





8. REFERENCE

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9. APPENDIX

Appendix A Visit Schedule (Part B of Study)

Study Cycles (21 days for one cycle)	**Screen[A]**	**C1**			**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10 onwards**	**End of treatment**	**28-day Follow-up[B]**	**Post progression survival F/U[C]**
Day	-28 to -1	1	8	15	1	1	1	1	1	1	1	1	1			3 monthly relative to progression
Informed consent	×															
Medical history and demographics	×	×														
Inclusion/exclusion criteria	×															
Physical examination	×	×			×	×	×	×	×	×	×	×	×	×		
ECOG PS	×	×			×	×	×	×	×	×	×	×	×	×		
Vital Signs (BP/HR)	×	×*	×	×	×*	×	×	×	×	×	×	×	×	×		
Body temperature	×	×			×	×	×	×	×	×	×	×	×	×		
Height	×															
Weight	×	×			×	×	×	×	×	×	×	×	×	×		
HBV, HCV, HIV screening[D]	×															
TB screening (PPD test or X-ray/CT)	×															
Brain MRI	×															
Pulmonary Function Tests[E]	×					×		×		×		×, then every 2 cycles				
Concomitant medications	×	×	=	=	=	=	=	=	=	=	=	=	=	×	×	
AE evaluation[F]	×	×	=	=	=	=	=	=	=	=	=	=	=	×	×	
12-lead ECG	×	×*	×	×	×*	×	×	×	×	×	×	×	×	×		
Echocardiogram/MUGA[G]	×					×				×, then every 4 cycles						

Study Cycles (21 days for one cycle)	**Screen[A]**	**C1**			**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10 onwards**	**End of treatment**	**28-day Follow-up[B]**	**Post progression survival F/U[C]**
Day	-28 to -1	1	8	15	1	1	1	1	1	1	1	1	1			3 monthly relative to progression
Hematology[H]	×	×	×	×	×	×	×	×	×	×	×	×	×	×		
Serum chemistry[H]	×	×	×	×	×	×	×	×	×	×	×	×	×	×		
Coagulation[H]	×	×	×	×	×	×	×	×	×	×	×	×	×	×		
Urinalysis[H]	×	×	×	×	×	×	×	×	×	×	×	×	×	×		
Pregnancy test (pre-menopausal females only)	×	×												×		
Tumor sample for pathology confirmation[I]	×															
Plasma PK[J]		×*		×	×*		×		×							
Whole blood for ex vivo pSTATs[K]		×*		×												
Blood sample for pharmacogenetics research (optional)[L]	×															
CT Scan (with contrast unless contraindicated)[M]	×					×			×			× , then every 3 cycles				
PET[N]	×					×										
Bone marrow aspiration and biopsy[O]	×															
AZD4205 administration[P]		×	=	=	=	=	=	=	=	=	=	=	×			
Survival[C]																×

Footnote for Schedule of Study Activities (Part B):

* Multiple time points. Details can be found in corresponding sections.

A. Screening tests should be performed within 28 days before the first administration of study drug.

B. A safety follow up visit will occur 28 days (±7) from the last dose of study drug.

C. In the Phase 2 expansion, following disease progression, the patient, patient's family, or the patient's current physician must be contacted every 3 months for survival information, for collection of details of subsequent treatment regimens received following withdrawal from study drug and to follow up unresolved AEs (unless the patient withdraws consent) regardless of date of last contact.
D. Both HBsAg and HBcAb should be negative for eligibility.
E. PFTs (including spirometry and DLCO) will be performed at screening, Cycle 3 Day 1 and then every 6 weeks and whenever clinically indicated.
F. AEs will be collected and recorded in CRF from first dosing of AZD4205 until the end of the follow up period (28 ±7 days post lase dose). However, SAE should be recorded in CRF from ICF signing to the end of defined follow-up period.
G. Echocardiogram or MUGA scan to assess LVEF will be conducted at screening (prior to first dose of AZD4205), Cycle 3 Day 1, then every 12 weeks for the rest of cycle.
H. In the Phase 2 expansion, laboratory tests for screening should be performed within 7 days prior to the planned first dosing date. In addition, laboratory tests do not need to be repeated at baseline if the baseline visit is within 3 days of the screening sample.
I. In the Phase 2 expansion, submission of the tumor block or unstained slides from a diagnostic biopsy is required for retrospective central confirmation of disease histologic subtype. The diagnostic specimen needs to be from a malignant lymph node or extra-nodal tissue obtained by excisional biopsy.
J. Patients at the selected sites will be invited for intense PK study on Cycle 1 Day 1 and Cycle 2 Day 1.
K. Blood sampling for pSTATs inhibition of blood cells is only mandatory for patients enrolled in the designated sites.
L. Blood sampling for pharmacogenetics research at screening is optional for patients enrolled in the Part B.
M. Pre-treatment tumor assessment should be performed within 28 days prior to (preferably close to) the first dose, including a computed tomography (CT) scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites (e.g., neck). During treatment, CT scans will be done for tumor assessments within 7 days of Day 1 of Cycle 3, 6, 9 and then every 3 cycles thereafter until PD.
N. PET scan, where available, needs to be performed for the pre-treatment tumor assessment. During the treatment, PET should be performed on Day 1 of Cycle 3 (within 7 days) and when need to confirm a complete metabolic remission, if FDG-avid disease is detected based on baseline PET scan. Patients with confirmed CR are not required to undergo further PET scans on study unless there is suspicion of progressive disease.
O. A bone marrow aspirate and biopsy will be done at screening (or within 60 days prior to the first dose of AZD4205). During treatment, bone marrow aspirate and biopsy will only be required to confirm any complete remission for patients with bone marrow involvement at baseline (screening) and when clinically indicated.
P. Treatment may continue until disease progression, unacceptable toxicity, discontinuation criteria have met, withdrawal of consent or termination of the study by Sponsor. All patients need to take prophylaxis for pneumocystis carinii pneumonia (PCP) infection per European Conference on Infections in Leukemia (ECIL).

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