A Modular Phase II, Open-label, Multicentre Study to Assess AZD4573 Efficacy and Safety as Monotherapy or in Combination with Anti-cancer Agents in Patients with Relapsed/Refractory Peripheral T-cell Lymphoma or classical Hodgkin Lymphoma

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STATISTICAL ANALYSIS PLAN	
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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
3L	Third-line
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutical Chemical
BMI	Body mass index
BOR	Best Overall Response
BSR	Baseline scaled ratio
BV	Brentuximab vedotin
cHL	Classical Hodgkin Lymphoma
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CR	Complete response
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DCO	Data cut-off
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FAS	Full analysis set
gCV	Geometric coefficient of variation
gMean	Geometric mean
gSD	Geometric standard deviation
IP	Investigational Product
IPD	Important protocol deviation
IPI	International Prognostic Index
ITT	Intent-to-Treat
IV	Intravenous

Abbreviation or Specialized Term	Definition
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NC	Not calculable
NE	Not evaluable
NK	Natural killer
NKTCL	Natural killer T-cell lymphoma
NS	No sample
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD1	Anti-programmed cell death-1
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
PTCL	Peripheral T-cell Lymphoma
r/r	Relapsed/refractory
RDI	Relative dose intensity
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System Organ Class
Std Dev	Standard deviation
TEAE	Treatment emergent adverse event
TFL	Tables, figures and listings
TLS	Tumour lysis syndrome
ULN	Upper limit of normal
WHO	World Health Organisation
WHODrug	World Health Organisation Drug Dictionary

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	**15-Mar-2022**	**Initial approved SAP**	**N/A**	**N/A**
Data presentation	20-Nov-2023	Added the interim response evaluable set in Section 4.2.2	N/A	This analysis set is currently not planned to be used for any outputs to be presented in the CSR. This analysis set will only be used for presentation in conferences and publications.
Data presentation	20-Nov-2023	Mention that SAP is for conference and publication purposes as well in Section 1	N/A	Details added to mention that this SAP is not only to describe CSR analyses, but also analyses performed for conferences and publications.
Data presentation	20-Nov-2023	Swimmer plot for response assessment added in Section 5.2.1.2	Yes	Visual representation of disease assessment results over time added for better understanding of the results.
Derivation of secondary endpoint(s)	20-Nov-2023	Added formula to derive QTcB in Section 5.6.10.1	Yes	QTcB was required for presentation per Version 1.0 of this document, but the formula was never provided.
Derivation of secondary endpoint(s)	20-Nov-2023	Clarified that duration of follow-up in overall survival should be derived for all participants and not just for censored participants in Section 5.2.5.2	Yes	Clarification provided to derivation provided in Version 1.0 of this document.
Derivation of secondary endpoint(s)	20-Nov-2023	Updated TLS monitoring derivations in Section 5.6.9	Yes	Consistency of text within the compound.
Other	20-Nov-2023	Removed imputation for missing best percentage change	Yes	Imputation does not make clinically sense.

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
		in target lesion in Section 5.2.1.3.1		
Data presentation	20-Nov-2023	Removed requirement to present ramp-up dosing in disposition Section 5.1.1.2	Yes	Not required per protocol and not adding any value in presentations.
Data presentation	20-Nov-2023	Update derivation of actual exposure in Section 5.6.1	Yes	Updated to be in line with standards as current derivations caused actual exposure to be longer than intended exposure.
Data presentation	20-Nov-2023	Update derivation of RDI and dose delays in Section 5.6.1 to account for windows around dosing	Yes	Added a statement that RDI should consider the ± 2 days window around doses. Dose delays were determined using 7 days between doses. Per a dosing window of ± 2 days around doses the calculation is updated to use 9 days instead of 7 days.
Data presentation	20-Nov-2023	Clarified that where we have missing post-baseline target lesions that these should not be presented in figures or summaries in Section 5.2.1.3	Yes	Missing target lesions underrepresent the target lesion sizes and changes at post-baseline timepoints.
Data presentation	20-Nov-2023	Clarified that highest ATC level should be used in summaries in Section 5.1.8.2	Yes	Clarification on what should be presented in summaries.
N/A	**20-Nov-2023**	**Approved SAP Version 2.0**	**N/A**	**N/A**
Data presentation	12-Dec-2023	Removed timepoint window derivations for safety endpoints from Section 4.1.3.2.	Yes	Due to the schedule of assessments in this study, it makes more sense to present results as recorded in the database as reassignment of

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
				visits caused confusion in interpretation of results.
N/A	**12-Dec-2023**	**Approved SAP Version 3.0**	**N/A**	**N/A**

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D8231C00001 supporting the clinical study report (CSR). Details provided in this document will also support the statistical analysis for conferences and publications. The reader is referred to the clinical study protocol (CSP) version 2 (dated 09 Sep 2021) and the electronic case report form (eCRF) for details of study conduct and data collection. While CSP version 3 (dated 16 Mar 2023) was released for use in some countries, it had no impact on the statistical analyses. The Statistical Analysis Plan (SAP) should not be read in isolation but in conjunction with the CSP.

2 STUDY DETAILS

The overarching primary hypothesis for this study is: AZD4573 will demonstrate anti-tumour efficacy, as monotherapy or in combination with other anti-cancer agents, in participants with either relapsed/refractory (r/r) Peripheral T-cell Lymphoma (PTCL) or r/r classical Hodgkin Lymphoma (cHL).

2.1 Module 1

2.1.1 Study Objectives

Table 1 Objectives and Endpoints – Module 1

Type	Objectives	Endpoints
Primary		
Efficacy	To assess the efficacy of AZD4573 by evaluation of objective response rate.	• Endpoint based on Lugano response criteria for malignant lymphoma (Cheson et al 2014) – ORR, defined as the proportion of participants who have a tumour response (CR or PR)[a]
Secondary		
Efficacy	To assess efficacy of AZD4573 by evaluation of tumour response and OS.	• Endpoints based on Lugano response criteria for malignant lymphoma (Cheson et al 2014) – CR rate – DoR – PFS • OS

Table 1 Objectives and Endpoints – Module 1

Type	Objectives	Endpoints
Safety	To assess the safety and tolerability of AZD4573.	Adverse events, laboratory data, vital signs, and ECG changes. Assessments related to AEs cover: • Occurrence/frequency • Relationship to IP as assessed by investigator • CTCAE grade • SAEs • Death • AEs leading to discontinuation of IP • AEs leading to dose modifications • AESIs
PK	To assess the plasma PK of AZD4573.	• Plasma concentrations and derived PK parameters for AZD4573
Exploratory		
PD	To assess the pharmacodynamics of AZD4573.	• CCI [redacted]
CCI [redacted]	CCI [redacted]	• CCI [redacted]
CCI [redacted]	CCI [redacted]	• CCI [redacted]

Table 1 Objectives and Endpoints – Module 1

Type	Objectives	Endpoints
Genetics	To collect and store CCI [redacted] CCI [redacted] sample, for future exploratory research CCI [redacted] CCI [redacted]	• CCI [redacted]

[a] By investigator assessment; however, if preliminary results suggest a major advance over available therapy, AstraZeneca will consult with relevant Health Authorities to agree on modifications to the protocol and will conduct blinded independent central review of ORR.

Abbreviations: AE, adverse event; CCI [redacted]; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DoR, duration of response; ECG, electrocardiogram; IP, investigational product; CCI [redacted] CCI [redacted]; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; CCI [redacted] CCI [redacted]; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; CCI [redacted] SAE, serious adverse event; TTR, time to response.

2.1.2 Study Design

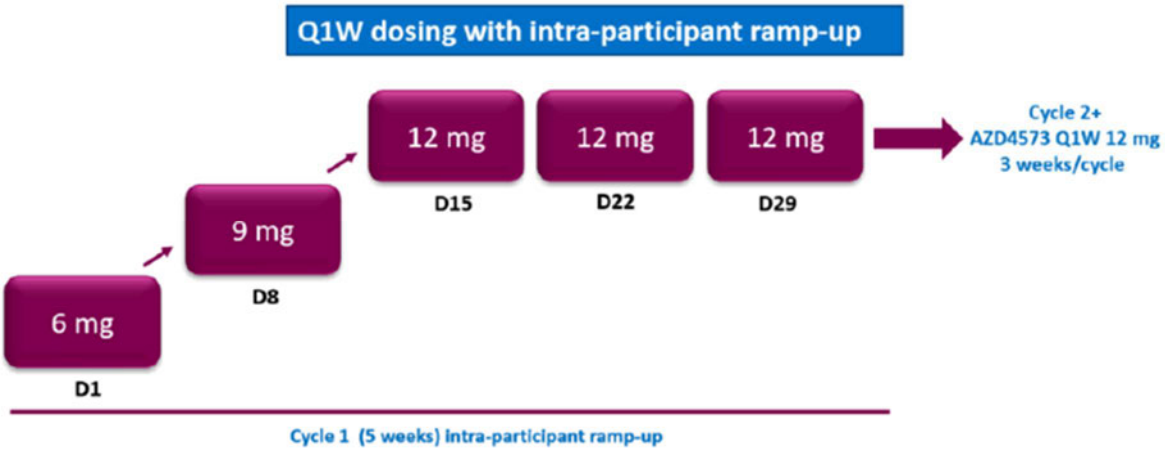
Module 1 will assess the efficacy of AZD4573 as a monotherapy in r/r PTCL and r/r cHL populations. Module 1 is non-randomised and will consist of 2 r/r PTCL cohorts (non-natural killer [NK] PTCL and natural killer T-cell lymphoma [NKTCL]) and one r/r cHL cohort.

During the first cycle per the protocol, participants will normally receive a single dose of AZD4573 once weekly, beginning with intra-participant ramp-up doses of 6 mg and 9 mg in Week 1 and Week 2, respectively. This is then followed by the target dose level of 12 mg for each of Weeks 3 to 5. It should be noted, however, that it may take more than 5 weeks to complete 3 AZD4573 dose weeks at target level, due to missed dose weeks and/or by repeating lower (ramp-up) doses of AZD4573. For the purposes of analysis defined in this SAP, Cycle 1 is defined as having received 5 doses of AZD4573 (regardless of dose level).

Each cycle beyond Cycle 1 will be 3 weeks in length and participants are planned to receive 12 mg infusions of AZD4573 once weekly until progression.

The dosing regimen for Module 1 is presented in Figure 1.

Figure 1 Module 1 AZD4573 Monotherapy Dosing Regimen in PTCL and cHL including Intra-Participant Dose Ramp-Up



3 CHANGES TO PROTOCOL PLANNED ANALYSIS

The CSP defines Cycle 1 as having a duration of 5 weeks. Section 2.1.2 of this SAP clarifies that Cycle 1 will only be considered completed once the participant has received 5 doses of AZD4573 (at any dose level).

Section 10.9.3 of the CSP defines the safety set as all participants who receive at least one dose of investigational product (IP) (study intervention). Participants who are exposed to any amount of IP, may have safety events, even if the full dose were not received (eg, dose interruption). Therefore, the safety population definition is updated to include all participants who received any amount of IP (Section 4.2.2).

A survival sweep for the purpose of analysing overall survival (OS) is currently not included in the CSP but is included in this version of the SAP (Section 5.2.5).

4 DATA ANALYSIS CONSIDERATIONS

4.1 Core

4.1.1 Timing of Analyses

The timing of analyses is specific to each module and are discussed separately for each module.

- Module 1: Section 4.2.1

4.1.2 Analysis Populations

The analysis populations are specific to each module and are discussed separately for each module.

- Module 1: Section 4.2.2

4.1.3 General Considerations

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

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

- Continuous endpoints will be summarised by the number of observations, mean, standard deviation (Std Dev), median, upper and lower quartiles (as applicable), minimum, and maximum. For data that requires log-transformation, it is more appropriate to present geometric mean (gMean), coefficient of variation (CV), median, minimum, and maximum. Categorical endpoints will be summarised by frequency counts and percentages for each category.
- Unless otherwise stated, percentages will be calculated out of the analysis set total, by cohort as appropriate. Percentages will not be presented for zero counts.
- For continuous data (except for pharmacokinetics [PK]), descriptive summary statistics (mean, median, quartiles, Std Dev, standard error, confidence intervals [CIs]) will be rounded to one additional decimal place compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data. Decimal precision for PK is described in Section 5.4.2.
- For categorical data, percentages will be rounded to one decimal place.
- Time to event variables will be presented using the Kaplan-Meier methodology where appropriate, including median time calculated from the Kaplan-Meier curves.
- For summaries at the participant level, all values will be included, regardless of whether they appear in a corresponding timepoint-based summary.
- SAS® version 9.4 (as a minimum) will be used for analyses presented in the CSR. PK parameters will be calculated using Phoenix® WinNonlin® Version 8.1 (as a minimum).

4.1.3.1 General Study Level Definitions

Baseline is the last non-missing value obtained prior to the first dose/administration of any IP and any information taken after first dose/administration of IP is regarded as post-baseline information. If 2 timepoints are equally eligible to assess participant status at baseline (eg, screening and baseline assessments both on the same date prior to first dose/administration

with no washout or other intervention in the screening period), the average is taken as the baseline value. For non-numeric laboratory tests (ie, some of the urinalysis parameters) where taking an average is not possible then the best value is taken as baseline as this is the most conservative. In the scenario where there are 2 assessments on Day 1 prior to first dose, one with time recorded and the other without time recorded, the one with time recorded is selected as baseline. Where safety data are summarised over time, study day is calculated in relation to date of first intervention of IP. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, serves as sufficient evidence that the assessment occurred prior to first dose. Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured is considered prior to the first dose. If no value exists before the first dose/administration, then the baseline value is treated as missing.

In all summaries, change from baseline variables will be calculated as the post-baseline value minus the value at baseline. The percentage change from baseline will be calculated as (post-baseline value – baseline value) / baseline value x100. For any endpoint subjected to log transformation, the change from baseline calculated and summarised on the log scale are back-transformed and presented as a 'baseline scaled ratio' (BSR). Percentage change is then calculated as (BSR – 1) x 100.

Study Day 1 is defined as the date of the first dose of IP (Cycle 1 Day 1). For timepoints (or events) that occur on or after first dose of IP, Study Day is derived as (date of timepoint [event] – date of first dose of IP +1). For timepoints (or events) that occur prior to first dose, Study Day is defined as (date of timepoint [event] – day of first dose of IP). There is no Day 0 defined for this study.

For listings (such as adverse events [AEs]) that include the derivation of "days since last dose", this is defined as (event date – date of last dose) where "date of last dose" is defined as the date of dosing immediately preceding the event occurrence. Events that occur on the same day as the last dose of IP will therefore be described as occurring 0 days from last dose of IP.

Study periods for the purpose of safety summaries will be defined as follows:

- Pre-treatment: Any result prior to first dose of IP.
- On-treatment: Any result from first dose of IP up to 30 days after last dose of IP, and prior to start of any subsequent cancer therapy.
- Follow-up: Any result after 30 days after last dose of IP, or after start of any subsequent cancer therapy.

For the purpose of summarising safety data assessed at timepoints, in addition to baseline data, only on-treatment data (as defined above) will be included in the summary tables.

Naming conventions of timepoints for inclusion in summary tables will be defined separately for each module.

- Module 1: Section 4.2.3.1

4.1.3.2 Timepoint Windows

For tumour assessments:

- The protocol assigned windows for tumour assessments will be used to assign the result to a particular timepoint.
- Examples applicable to each module will be defined separately for that module.
  - Module 1: Section 4.2.3.2

For safety assessments:

- Results will be presented as recorded in the database and no windowing to assign the result to a particular timepoint will be done.

4.1.3.3 Handling of Unscheduled Timepoints

Unscheduled timepoints will be included in listings but will not be included in by-timepoint summaries. Unscheduled timepoints have the potential to be included in summaries showing the maximum or minimum values while on IP.

4.1.3.4 Multiplicity/Multiple Comparisons

The handling of multiplicity/multiple comparisons is specific to each module and are discussed separately for each module.

- Module 1: Section 4.2.3.4

4.1.3.5 Handling of Protocol Deviations in Study Analysis

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

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

- Patients who deviate from entry criteria per CSP

- No baseline Lugano assessments on or before the date of first dose
- Received prohibited concomitant medications or therapies
- Participants deviating from prescribed dosing regimen
- Missed timepoints, assessments, or treatments that, in the opinion of the investigator, were due to Coronavirus Disease 2019 (COVID-19) global pandemic, and where there was a significant effect on either completeness, accuracy and/or reliability of the participant's data, or the participant's rights, safety or wellbeing
- Missing scheduled efficacy assessments
- Deviation from Good Clinical Practice as determined by medical review (for example insufficient informed consent)

A detailed list of protocol deviations to be considered are defined in the study specific protocol deviation specifications.

Participants with no baseline Lugano assessments will be excluded from the response evaluable set. None of the other deviations defined in this study will lead to participants being excluded from any analysis populations described in this SAP. If a deviation is serious enough to have a potential impact on the primary analysis, sensitivity analyses may be performed. The need for such a sensitivity analysis will be determined following review of the protocol deviations ahead of database lock and will be documented prior to the analysis being conducted.

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

4.1.3.6 Missing Dates

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

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

- For missing diagnostic dates (eg, disease diagnosis), if the day and/or month are missing use 01 and/or January. If year is missing, put the complete date to missing.
- For missing AE and concomitant medication start dates, the following is applied:
  - Missing day – impute the 1st of the month unless month is the same as month of the first dose of the study drug then impute first dose date.
  - Missing day and month – impute 1st January unless year is the same as first dose date then impute first dose date.

  - Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st of January of the same year as the end date.
  - Imputed start date should be no later than the end date.
- For missing AE and concomitant medication end dates, the following is applied:
  - Missing day – impute the last day of the month unless both the month and year are the same as the last dose date or the primary analysis date cut-off (DCO) date then impute the last dose date or the primary analysis DCO date.
  - Missing day and month – Impute 31st December unless the year is the same as the last dose date or the primary analysis DCO date then impute the last date or the primary analysis DCO date.
  - Completely Missing – before imputing a date, consider whether the AE/medication is still ongoing and also when it started in relation to study drug. If the ongoing flag is missing then assume that AE is still present/ medication is still being taken (ie, do not impute a date). If the AE/medication has stopped and start date is prior to first dose date, then impute first dose date. Or if it started on or after first dose date then impute a date that is after the last dose of study drug date.
- Flags will be retained in the database indicating where any programmatic imputation has been applied, and in such cases for AEs and concomitant medications, any durations will not be calculated.

4.1.3.7 Sample Size

Sample size is specific to each module and is discussed separately for each module.

- Module 1: Section 4.2.3.7

4.2 Module 1

4.2.1 Timing of Analyses

The DCO for the primary analysis for each Module 1 PTCL cohort (Cohorts 1 and 2) will occur after 21 response-evaluable participants in the cohort have had the opportunity to be followed for at least 6 months since their first dose or have progressed or have initiated other anticancer therapy, or when 75% of participants have progressed or died, whichever occurs first. If one cohort reaches its planned primary analysis DCO ahead of the other, then the slower enrolling cohort may be evaluated for efficacy responses at the same time. The purpose of evaluating the slower cohort early would be for internal planning and to review continued development of the AZD4573 in one or both r/r PTCL groups. When both cohorts have reached their primary analysis DCOs the efficacy and safety data may be pooled for analysis. Additional data cuts may also be performed, if required.

The DCO for primary analysis of the Module 1 cHL Cohort (Cohort 3) will occur after 21 response-evaluable participants in the cohort have had the opportunity to be followed for at least 6 months since their first dose or have progressed or have initiated other anticancer therapy, or when 75% of participants have progressed or died, whichever occur first. Additional data cuts may also be performed, if required.

At the end of the module a final analysis will be conducted to incorporate all data (up to and beyond the primary analysis) from all participants.

4.2.2 Analysis Populations

For purposes of analysis, the study populations are defined as provided in Table 2.

All participants who received any amount of IP will be included in the safety population.

The following populations are defined:

Table 2 Populations for Analyses

Population/Analysis set	Description	Endpoint/Output
Enrolled	All participants who sign the ICF.	Disposition
Safety	All participants who receive any amount of any IP.	Exposure Safety PK concentrations and parameters listings
Full analysis set/ITT	All participants who receive any amount of any IP.	Baseline and demography PFS OS
Response evaluable	All dosed participants who have measurable disease at baseline.	ORR CR DoR
Interim response evaluable	All dosed participants with measurable disease at baseline that have had their first post-baseline disease assessment performed or have discontinued study treatment before the first post-baseline disease assessment. This analysis set will not be used for presentation in the CSR and is only defined for conferences and publications.	ORR at interim DoR at interim
PK	All participants who receive any amount of IP with at least one reportable concentration.*	PK concentrations PK parameters

Abbreviations: ICF, informed consent form; IP, investigational product; ITT, intention-to-treat; PK, pharmacokinetics; PFS, progression free survival; OS, overall survival; DoR, duration of response; ORR, objective response rate; CR, complete response.
* Individual PK concentration and parameter data values that are excluded from the descriptive summary tables and/or figures eg, due to important protocol deviations that might effect PK – are included in the listings and are flagged with an appropriate footnote.

4.2.3 General Considerations

4.2.3.1 General Study Level Definitions

Refer to Section 4.1.3.1.

Timepoint naming conventions are defined separately for efficacy and non-efficacy data.

Timepoints for efficacy summaries will be named according to the time from first dose as defined in the CSP. Examples are:

- After 8 weeks
- After 17 weeks
- After 26 weeks
- End of Treatment
- 30-day follow-up visit

Non-efficacy data will be named as in the database.

4.2.3.2 Timepoint Windows

Refer to Section 4.1.3.2.

4.2.3.3 Handling of Unscheduled Timepoints

Refer to Section 4.1.3.3.

4.2.3.4 Multiplicity/Multiple Comparisons

Not applicable.

4.2.3.5 Handling of Protocol Deviations in Study Analysis

Refer to Section 4.1.3.5.

4.2.3.6 Missing Dates

Refer to Section 4.1.3.6.

4.2.3.7 Sample size

Refer to Section 10.9.2 of the CSP for detailed information on the sample size for module 1.

Table 3 Sample Size: Module 1

Indication	Primary Analysis Sample Size	CCI
PTCL	Cohort 1: Non-NK PTCL, N = 21 response-evaluable	
	Cohort 2: NKTCL, N = 21 response-evaluable	
cHL	Cohort 3: cHL, N = 21 response-evaluable	

CCI

Abbreviations: cHL, classical Hodgkins lymphoma; NKTCL, natural killer T-cell lymphoma; non-NK PTCL; non-natural killer peripheral T-cell lymphoma; PTCL, peripheral T-cell lymphoma; CCI

In Module 1 the primary objective is to evaluate efficacy of AZD4573 monotherapy in non-NK PTCL, NKTCL and cHL. For primary objective response rate (ORR) endpoint analyses approximately 21 recommended phase 2 dose (RP2D)-treated response-evaluable participants will be incorporated per cohort. These sample sizes are large enough to give a reasonable chance of detecting an efficacy signal.

Historical response rates for drugs approved for r/r PTCL 2L are in the range of 25% to 30% (Zain 2019).

The following examples give an indication of the level of precision that will be achieved at the primary analysis for PTCL within and across Module 1 Cohorts 1 and 2 of this study:

Table 4 CCI

CCI

Historical response rates in r/r cHL third-line (3L) (excluding brentuximab vedotin [BV] and anti-programmed cell death -1 [PD1]) have been in the range of 10% to 50% (Vassilakopoulos et al 2020)

The following examples give an indication of the level of precision that will be achieved for cHL in Module 1 Cohort 3 of this study:

Table 5 CCI

CCI

[redacted]

5 STATISTICAL ANALYSIS

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

5.1 Study Population

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

5.1.1 Subject Disposition and Completion Status

5.1.1.1 Definitions and Derivations

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

Study participant (ie, a participant is "enrolled") is defined as having a signed informed consent available.

The end of study and end of module is defined in the CSP Section 4.4.

5.1.1.2 Presentation

Participant disposition including screen failures and reason for screen failures will be listed and summarised for all participants enrolled by cohort as defined by the current relevant

tables, figures and listings (TFL) standards. The number and percentage of participants for the following will be summarised:

- Participants screened;
- Screen failures;
- Participants assigned to IP;
- Participants assigned to IP, but who were not treated;
- Participants who received IP and participants who did not receive IP;
- Participants ongoing IP at DCO;
- Participants who discontinued IP;
- Participants ongoing study at DCO;
- Participants who terminated study.

Summaries on disposition due to COVID-19 will be added to the disposition table if applicable. The number and percentage of participants for the following summaries will be added if applicable:

- Participants who discontinue IP due to COVID-19;
- Participants who withdrew from study due to COVID-19.

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

5.1.2 Analysis Sets

5.1.2.1 Definitions and Derivations

For the definitions of each analysis set, refer to Section 4.1.2.

5.1.2.2 Presentation

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

5.1.3 Protocol Deviations

5.1.3.1 Definitions and Derivations

Protocol deviations are defined in Section 4.1.3.5.

5.1.3.2 Presentation

The incidence of IPDs will be summarised for the full analysis set (FAS) by deviation categories. The number and percentage of participants in the following categories will be summarised:

- Number of participants with at least one IPD
- Number of participants with at least one COVID-19 related IPD
- Number of participants with at least one IPD, excluding COVID-19 related IPDs.

A listing will be provided with IPD details.

5.1.4 Demographics

5.1.4.1 Definitions and Derivations

Age will be grouped accordingly in the following categories: ≥ 18 – 64, ≥ 65 – 74, ≥ 75 – 84, and ≥ 85. Each race category counts participants who selected only that category.

5.1.4.2 Presentation

Demographics will be summarised and listed based on the FAS by cohort as defined by the current relevant TFL standards. The following will be summarised: age, age group, sex, race, and ethnicity.

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

The number of participants recruited in each country and each center will be presented by analysis populations.

5.1.5 Baseline Characteristics

5.1.5.1 Definitions and Derivations

Body mass index (BMI) will be derived as:

$$\mathrm{BMI}(\mathrm{kg/m^2}) = \frac{\mathrm{weight(kg)}}{\mathrm{height(m)}^2}$$

5.1.5.2 Presentation

Baseline characteristics will be listed and summarised for the FAS by cohort as defined by the current relevant TFL standards. The following will be summarised: height, weight and BMI.

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

5.1.6 Disease Characteristics

5.1.6.1 Presentation

Disease characteristics at baseline will be summarised and listed for all participants in the FAS by cohort as defined by the current relevant TFL standards.

Summaries will be produced that present:

- Eastern Cooperative Oncology Group (ECOG) performance status
- Lymphoma diagnosis:
  - Primary tumour location (lymph node/ extranodal)
  - Histology type (lymphoma)
  - Lymphoma type
  - Location of involvement (brain, spleen, bone marrow, liver and extranodal)
  - Presence of bulky nodal disease
  - Ann Arbor Lymphoma staging
  - Ann Arbor Lymphoma symptoms
  - International Prognostic Index (IPI) score
- cHL pathology
  - Primary tumour location (axilla/ inguinal region/ mediastinum/ mesenteric/ naso-oropharynx/ neck/ para-aortic/ Waldeyer's ring or tonsil/ other)
  - Ann Arbor Lymphoma staging
  - Ann Arbor Lymphoma symptoms

5.1.7 Medical History and Concomitant Disease

5.1.7.1 Definitions and Derivations

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 (as a minimum).

5.1.7.2 Presentation

Medical history, surgical history and concomitant disease will be listed and summarised for the FAS by cohort as defined by the current TFL standards.

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

The number and percentage of participants who have had prior cancer therapies will be summarised by Anatomical Therapeutic Chemical (ATC) classification and generic drug name, coded by World Health Organization (WHO) – Drug dictionary (WHO Drug Global B3 Sep 2021 or later).

Summaries for the number and percentage of participants who had a certain number of previous lines of therapies and the best response on most recent line of therapy will be produced.

Summaries on participants' medical history by System Organ Class (SOC) and Preferred Term (PT) will be produced.

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

5.1.8 Prior and Concomitant Medications

5.1.8.1 Definitions and Derivations

For the purpose of inclusion in prior and/ or concomitant medication or therapy summaries, incomplete dates will be imputed as detailed in Section 4.1.3.6.

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

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

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

5.1.8.2 Presentation

The number and percentage of participants who took prior and concomitant medications will be summarised by ATC classification codes (highest level) and the generic term coded by WHODrug Global B3 Sep 2021 or later for the FAS by cohort.

A summary of disallowed concomitant medications will be produced. All prior, concomitant and post-treatment medication data will be listed.

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

5.2 Endpoint Analyses – Module 1

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

Table 6 Endpoint Analyses: Module 1

Statistical category	Endpoint	Population	Population level summary (analysis)	Details in section
Objective 1: To assess the efficacy of AZD4573 by evaluation of ORR				
Primary	ORR	Response evaluable	ORR including 80% and 95% 2-sided exact binomial CI	5.2.1
Objective 2: To assess the efficacy of AZD4573 by evaluation of tumour response and OS				
Secondary	CR	Response evaluable	CR rate including 80% and 95% 2-sided exact binomial CI	5.2.2
Secondary	DoR	Response evaluable	Median DoR and 2-sided 80% and 95% CIs estimated using the Kaplan-Meier method	5.2.3
Secondary	PFS	FAS	Median PFS and its 2-sided 80% and 95% CIs estimated using the Kaplan-Meier method	5.2.4
Secondary	OS	FAS	Median OS and its 2-sided 80% and 95% CIs estimated using the Kaplan-Meier method	5.2.5

Table 6 Endpoint Analyses: Module 1

Statistical category	Endpoint	Population	Population level summary (analysis)	Details in section
Objective 3: To assess the safety and tolerability of AZD4573				
Secondary	AEs, laboratory data, vital signs, and ECG changes	Safety analysis set	Descriptive statistics on safety endpoints	5.6.2 (AEs) 5.6.4 and 5.6.5 (laboratory data) 5.6.6 (vital signs) 5.6.10 (ECG)
Objective 4: To assess the plasma PK of AZD4573				
Secondary	Plasma concentration and derived PK parameters for AZD4573	PK analysis set	Descriptive statistics on PK endpoints	5.4

Abbreviations: AE, adverse event; CI, confidence interval; CR, complete response; DoR, duration of response; ECG, electrocardiogram; FAS, full analysis set; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PK, pharmacokinetic.

Efficacy analyses, except for OS, will be based on investigator assessments (as entered in the database) based on Lugano criteria for malignant lymphoma (Cheson et al 2014).

All efficacy results will be listed.

All efficacy analyses will be presented by cohort.

5.2.1 Primary Endpoint – Objective Response Rate (ORR) by Lugano

The primary endpoint for Module 1 is ORR based on Lugano criteria for malignant lymphoma.

5.2.1.1 Definition and Derivations

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

Data obtained from first dose up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who discontinue IP without a response or progression, receive a subsequent anti-cancer therapy and then respond will not be included as

responders in the ORR (ie, the timepoint contributing to a response must be prior to subsequent therapy for the participant to be considered as a responder).

The ORR will be based on the investigator assessment using all scans, regardless of whether the scan was scheduled or not.

In addition, best overall response will be calculated based on overall timepoint responses from Lugano assessments by the investigator recorded in the eCRF. It is the best response a participant has had following start of IP, but prior to starting any subsequent cancer therapy and up to and including Lugano progression or the latest evaluable assessment in the absence of Lugano progression. Categories of BOR will be based on Lugano criteria using the following response criteria (CR, PR, stable disease [SD], progressive disease [PD], not evaluable [NE], and unknown).

5.2.1.2 Primary Analysis of Primary Endpoint: ORR

Summaries will be produced that present the number and percentage of participants with a tumour response (CR/PR) based upon the number of participants in the response evaluable analysis set. ORR will be calculated and binomial exact 2-sided CIs at 80% and 95% will be presented for participants in the response evaluable set. For the purpose of conferences and publications, outputs may also be presented for the interim response evaluable set.

A swimmer plot will be presented showing disease assessment results for each assessment performed, including treatment duration and treatment status.

In addition, BOR will be summarised by number of participants and percentage for each category (CR, PR, SD, PD, and NE). No formal statistical analyses are planned for BOR.

5.2.1.3 Supportive Data: Change in Target Lesion Tumour Size

Change in target lesion tumour size will be analysed as supportive to the primary endpoint and is not a specified endpoint of this study.

5.2.1.3.1 Definition and Derivation: Change in Target Lesion Tumour Size

Target lesions are measurable tumour lesions. Baseline is defined to be the last evaluable assessment prior to starting intervention.

Target lesion tumour size for the target measurable nodes and extra-nodal sites at any timepoint is defined as the sum of the product of the perpendicular diameters for multiple lesions. When a lesion is too small to measure, 5 mm x 5 mm will be assigned as the product of the perpendicular diameters.

If target lesion measurements are missing post-baseline then the sum of the product of perpendicular diameters for multiple lesions will be set to missing for that post-baseline

measurements. Subsequent percentage changes will consequently not be calculated using post-baseline measurements where any target lesion measurement is missing.

The percentage change in target lesion size at each timepoint for which data are available will be obtained for each participant.

The best change in tumour size from baseline (ie, depth of response) is the largest decrease from baseline or the smallest increase from baseline in the absence of a reduction and includes all assessments:

- up to and including the first timepoint at which the overall timepoint response is a PD,
- prior to death in the absence of progression,
- prior to the start of subsequent anti-cancer therapy,
- or up to and including the last evaluable tumour assessment if the participant has not died, progressed or stated subsequent anti-cancer therapy.

5.2.1.3.2 Primary Analysis of Supportive Data: Change in Target Lesion Tumour Size

Only participants included in the response evaluable analysis set will be included in summaries of change in tumour size. For the purpose of conferences and publications, this may be presented for participants in the interim response evaluable set.

The target lesion tumour size and percentage change from baseline in target lesion tumour size will be summarized using descriptive statistics and presented at each scheduled timepoint (refer to efficacy naming conventions in Section 4.2.3.1 and Section 8 Appendix A). Participants who progress before the scheduled assessment at 8 weeks should have had a tumour assessment performed at the time of progression prior to treatment discontinuation. The tumour size from their latest progression assessment is used instead of the 8-week assessment for these participants.

Additionally, using all scheduled and unscheduled tumour assessments, ‘spider’ plots of percentage change from baseline in target lesion size by participants will be presented. A graphical summary of the best percentage change in target lesion tumour size will be presented in a vertical bar chart with each participant’s best percentage change from baseline to nadir displayed as a vertical bar, with colour coding that indicates best response obtained (“waterfall” plot).

5.2.2 Secondary Endpoint: Complete Response Rate (CR Rate)

CR is a secondary endpoint.

5.2.2.1 Definition and Derivations

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

5.2.2.2 Primary Analysis of Secondary Endpoint: CR Rate

CR rate will be calculated and binomial exact 2-sided CIs at 80% and 95% will be presented for participants in the response evaluable set.

5.2.3 Secondary Endpoint: Duration of Response (DoR)

DoR is a secondary endpoint.

5.2.3.1 Definition

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

5.2.3.2 Derivations

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

The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response is defined as the latest of the dates contributing towards the first timepoint response of CR or PR. If a participant does not progress following a response, then their DoR is censored on the PFS censoring date. Only participants who have achieved objective response are evaluated for DoR.

5.2.3.3 Primary Analysis of Secondary Endpoint: DoR

Only participants who achieved objective response (CR or PR) will be included in the summaries of DoR. If number of responders allow, Kaplan-Meier plots of DoR will be presented. The median DoR and 2-sided 80% and 95% CIs will be estimated using the Kaplan-Meier method.

Swimmer plots by participant (including non-responders) will be created to visualise when response begins and ends and when study intervention is withdrawn.

5.2.4 Secondary Endpoint: Progression-free Survival (PFS)

PFS is a secondary endpoint.

5.2.4.1 Definition

PFS is defined as the time from first dose until the date of first documented disease progression, per Lugano classification as assessed by the investigator at local site, or death (by

any cause in the absence of disease progression), regardless of whether the participant withdraws from therapy or receives another anti-cancer therapy prior to Lugano progression.

5.2.4.2 Derivations

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

Participants who have not progressed or died at the time of analysis, or have unknown status, are censored at the time of the latest date of assessment from their last evaluable disease assessment. However, if the participant progresses or dies immediately after 2 or more consecutive missed timepoints, the participant is censored at the time of the latest evaluable disease assessment prior to the 2 missed timepoints. Note: a NE timepoint is not considered as a missed timepoint.

Given the schedule timepoint assessment scheme (ie, 9-weekly for the first 26 weeks then 12-weekly thereafter) the definition of 2 missed timepoints will change.

If the previous assessment is less than study day 113 (ie, week 16) then 2 missing timepoints will equate to 20 weeks since the previous assessment, allowing for early and late timepoints (ie, 2 x 9 weeks + 1 week for an early assessment + 1 week for a late assessment= 20 weeks).

If the 2 missed timepoints occur over the period when the scheduled frequency of assessment changes from nine-weekly to twelve-weekly this will equate to 23 weeks (ie, take the average of 9 and 12 weeks which gives 10.5 weeks and then apply the same rationale, hence 2 x 10.5 weeks + 1 week for early assessment + 1 week for late assessment =23 weeks). The time period for the previous assessment is from study days 113 to 175 (ie, week 16 to week 25).

From week 25 onwards (when the scheduling changes to 12-weekly assessments), 2 missing timepoints equates to 26 weeks (ie, 2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment = 26 weeks).

If the participant has no evaluable disease assessments post-baseline or does not have baseline assessment data, they will be censored at Day 1 unless they die within 2 timepoints of baseline (19 weeks plus 1 week allowing for a late assessment within the timepoint window) when the death date qualifies as a PFS event.

A summary of censoring rules and the date of PD/death or censoring are given in Table 7.Note that censoring overrides event in certain specified cases and that this table does not indicate the order for programming.

Table 7 Summary of Censoring Rules for PFS

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

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

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

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

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

Note: for target lesions only the latest scan date is recorded out of all scans performed at that assessment for the target lesions and similarly for non-target lesions only the latest scan date is recorded out of all scans performed at that assessment for the non-target lesions.

Duration of follow-up for PFS is applicable only for PFS censored participants and is defined as follows:

Duration of follow-up for PFS in censored participants (months) = (date of PFS censoring – date of first dose + 1) / (365.25/12).

5.2.4.3 Primary Analysis of Secondary Endpoint: PFS

The main analysis of PFS is based on the FAS. The number and percentage of participants experiencing a PFS event (broken down by type of event/censoring) and Kaplan-Meier plots of PFS will be presented. The median PFS and its 2-sided 80% and 95% CIs will be estimated using the Kaplan-Meier method (if participant numbers allow).

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

A summary of the duration of follow-up for PFS is included using median (range) for censored participants (including all types of PFS censoring).

The proportion of participants alive and progression free at every 3 months (3, 6, 9, 12, etc.) and associated 2-sided 80% and 95% CIs will be estimated using the Kaplan-Meier method.

5.2.4.4 Sensitivity Analysis of PFS Endpoint

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

Separately, a sensitivity analysis will also be conducted to assess the impact of COVID-19 related deaths on PFS. That is, participants who had a PFS event due to death where the primary or secondary cause of death was COVID-19 infection or COVID-19 infection was reported as a fatal AE, will be censored on the last available tumour assessment prior to COVID-19 infection related death. This sensitivity analysis will only be performed if 5 or more participants have confirmed or suspected COVID-19 death events.

5.2.5 Secondary Endpoint: Overall Survival (OS)

OS is a secondary efficacy endpoint.

5.2.5.1 Definition

OS is defined as the time from the date of first dose until death due to any cause regardless of whether the participant withdraws from study therapy or receives another anti-cancer therapy.

5.2.5.2 Derivations

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

Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive. Participants known to be alive or dead after the DCO for analysis will be censored at the DCO. Participants lost to follow-up will be censored at the date the participant is last known to have been alive. At study closure, any participant still alive after last patient last visit for the study will be censored at the date of last patient last visit.

Note: Survival calls will be made in the week following the date of DCO for the analysis, and if participants are confirmed to be alive or if the death date is after the DCO date these participants will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and "lost to follow-up" participants at the time of the final OS analysis should be obtained by the site personnel by checking the participant's notes, hospital records, contacting the participant's general practitioner and checking publicly-available death registries. In the event that the participant has actively withdrawn consent to the processing of their personal data, the vital status of the participant can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

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

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

Duration of follow-up for OS is reported separately for censored participants and non-censored participants as well as combined for all participants and is defined as follows:

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

5.2.5.3 Handling of Dropouts and Missing Data

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

- For Missing day only – using the 1st of the month of death.
- For Missing day and Month – using the 1st of January of the year of death.

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

5.2.5.4 Primary Analysis of Secondary Endpoint (Overall Survival)

The analysis of OS is based on the FAS. The number and percentage of participants experiencing an OS event and Kaplan-Meier plots of OS will be presented. The median OS and 2-sided 80% and 95% CIs will be estimated using the Kaplan-Meier method (if participant numbers allow).

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

A summary of the duration of follow-up for OS will be included using median (range). This is presented separately for censored and non-censored participants.

The proportion of participants alive at every 3 months (3, 6, 9, 12, etc.) and associated 2-sided 80% and 95% CIs will be estimated using the Kaplan-Meier method.

5.2.5.5 Sensitivity Analysis of OS Endpoint

A sensitivity analysis will also be conducted to assess the impact of COVID-19 related deaths on OS. That is, participants who had an OS event due to death where the primary or secondary cause of death was COVID-19 infection or COVID-19 infection was reported as a fatal AE, will be censored on the date of their COVID-19 infection related death. This sensitivity analysis will only be performed if 5 or more participants have confirmed or suspected COVID-19 death events.

5.3 Pharmacodynamic Endpoints [redacted]

Analysis on pharmacodynamic [redacted] will be described in a separate analysis plan.

5.4 Pharmacokinetics – Module 1

This section covers details related to PK endpoints and analyses. PK is a secondary endpoint for Module 1.

5.4.1 Definition and Derivations

5.4.1.1 Plasma

The PK parameters of the concentration data for AZD4573 and its metabolites (if applicable) will be derived using non-compartmental methods in Phoenix® WinNonlin® Version 8.1 or higher (Certara) as data applicable.

The PK parameters will be 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 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.

For AZD4573 (intravenous [IV] infusion) the following PK parameters will be calculated using the PK concentration vs. time data from Cycle 1, Day 1 of Weeks 1 through 3 and Cycle 2, Day 1.

Cmax	Maximum observed plasma (peak) drug concentration
tmax	Time to reach peak or maximum observed concentration following IP administration
λz	Terminal rate constant, estimated by log-linear least squares regression of the terminal part of the concentration-time curve
t1/2	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
AUC(0-24)	Area under the plasma concentration-time curve from 0 to time 24 hours
AUClast	Area under the plasma concentration-time curve from zero to last quantifiable concentration

AUCinf	Area under plasma concentration-time curve from zero to infinity
CL	Total body clearance of drug from plasma after a single IV infusion dose
Vz	Volume of distribution after a single IV infusion (based on terminal phase)
Vss	Volume of distribution at steady-state after a single IV infusion
tlast	Time of last observed (quantifiable) concentration
Cmax/D	Dose-normalised Cmax
AUClast/D	Dose-normalised AUClast
AUCinf/D	Dose-normalised AUCinf

Additional PK parameters may be determined where appropriate.

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)
λz span ratio	Time period over which λz was determined as a ratio of t1/2λz
AUCextr	Extrapolated area under the curve from tlast to infinity (%)

The time period used for the estimation of apparent terminal elimination half-lives, where possible, should be over at least 2 half-lives. For t1/2 estimates where λz was calculated over a time period less than twice their resultant half-life, the reliability of t1/2 and any PK parameters derived from λz will be discussed in the CSR.

5.4.1.2 CCI

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5.4.2 Primary Analysis of Pharmacokinetics

5.4.2.1 Plasma

Plasma concentrations will be listed by actual and relative (to dose administration) sampling time. The following summary statistics will be presented for concentrations and PK parameters at each time point:

- n below LLOQ (only for concentrations)
- gMean (calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)

- Geometric CV% (gCV, calculated as $100\times\sqrt{\exp(s^2)-1}$ where s is the standard deviation of the data on a natural log scale)
- Gmean + gSD (gSD calculated as exp[s] where s is the standard deviation of the data on the natural log scale. Gmean + gSD calculated as $\exp(\mu+s)$)
- Gmean – gSD (calculated as $\exp(\mu-s)$)
- Arithmetic mean
- Arithmetic Std Dev
- Minimum
- Median
- Maximum
- Number of observations

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

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

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

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

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

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

The following figures, in black and white, will be produced:

- Participant Profiles, Plasma Concentration Time Data – Linear Scale

- Participant Profiles, Plasma Concentration Time Data – Semi-logarithmic Scale
- Gmean (± gSD), Plasma Concentration Time Data
- Gmean, Plasma Concentration Time Data – Semi-logarithmic scale

Individual and spaghetti figures will be plotted using concentration versus actual time, and mean figures will be plotted using concentration time versus nominal time by PK day as needed.

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

- Individual PK parameters will be presented to 4 significant digits, with the exception of tmax, which will be presented to 2 decimal places.
- Parameters derived directly from source data (eg, Cmax) will be reported with the same precision as the source data (if this is not 4 significant digits).
- The mean, gMean, median and Std Dev values will be reported to 4 significant digits, all other descriptive statistics will be reported to 3 significant digits except for gCV% which will be presented to one decimal place.
- For tmax, the minimum and maximum will be presented to 2 decimal places and all other descriptive statistics will be presented to 3 decimal places.
- Estimates and confidence intervals in the form of percentages will be presented to 2 decimal places.

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

For the non-compartmental analysis and individual plots, if a BLQ value occurs before the first measurable concentration, it will be assigned the value of 0, otherwise it will be treated as missing. The following rules apply with special situations defined below:

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

Treatment of Outliers in Pharmacokinetic Analysis

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

Quantifiable predose concentration values in the first dosing of Cycle 1 will be considered anomalous and set to missing for the PK analysis.

5.4.2.2 CCI

CCI

5.5 Immunogenicity

No immunogenicity analysis will be conducted for Module 1.

5.6 Safety Analyses

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

Tables will be provided for the safety analysis set; listings will be provided for All participants or the safety set depending on the availability of data.

All safety analysis will be presented by cohort.

5.6.1 Exposure

Exposure amounts, durations and dose modifications and interruptions/delays will be summarised for the following periods:

- Overall treatment period
- Cycle 1
- Up to first tumour assessment
- Cycle 2 onwards

5.6.1.1 Definitions and Derivations

- Total duration of exposure is defined by the last date of actual AZD4573 dosing (ie, a dose > 0 mg was given) plus 6 days (due to the fact that AZD4573 is ordinarily dosed on a weekly schedule) minus the date of first AZD4573 dose (> 0 mg) plus 1.
  - For participants who die whilst on study treatment or if a DCO occurs, duration of exposure (months/weeks) is defined as date of death/DCO (whichever occurs first) minus the date of first treatment plus 1 day.

  - Therefore: Duration of exposure (weeks) = [min(last dose date where dose > 0 mg + 6, date of death, date of DCO) – first dose date + 1]/7.

- Actual duration of exposure (weeks) = [duration of exposure (days) – total duration of dose delays (days)]/7. Duration of exposure is calculated as above, and dose delays are defined as any length of time where the subject has not taken any of the planned dose in accordance with the protocol. The actual exposure calculation makes no adjustment for any dose reductions that may have occurred.
- Dose intensity of study intervention is addressed by considering relative dose intensity (RDI), where RDI is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. More specifically, RDI is defined as follows:
  - RDI (%) = 100 × d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the actual last day of dosing. D is the total dose that would be delivered, if there were no modification to dose or schedule. Note: When accounting for the calculation of intended cumulative dose 2 days should be added to the date of last dose to reflect the protocol allowed window for dosing.
  - CCI [redacted]
- Duration of dose delays will be derived for doses indicated as being delayed on the eCRF. For each individual dose, the duration of dose delay is the number of days the dose was received outside of the original planned dosing schedule. Overall duration of dose delays will be calculated as the sum of all individual dose delays during the study. For example, assume the eCRF indicate that there was a treatment delay (question "Treatment delayed" indicated as "Y" by investigator) then the duration of the individual delay will be [date first dose received after delay – date last dose received before delay – 9]. For example, if dose is given on days 1 and 15 with the eCRF indicating a delay, the duration of the delay = 15 – 1 – 9 = 5 days.

5.6.1.2 Presentation

Total and actual duration of exposure to study intervention in weeks will be summarised by descriptive statistics. Dose intensity will be summarised by descriptive statistics. Exposure to IP (ie, total amount of IP received) will be listed and summarised for all subjects. Exposure swimmer plot(s) will be produced, with a line presented for each subject to display relevant exposure and disposition details.

Dosing deviations for IP will be summarized with reasons for deviations for the following categories: reductions and interruptions. The number of subjects with dosing delays and total dose delays will be summarised. Dose delays will also be summarised for number of delays with a duration < 7 days and number of delays with a duration ≥ 7 days.

The following additional summaries will also be produced:

- Number of participants that completed Cycle 1 (ie, received 5 doses of AZD4573), including number of participants that did not complete Cycle 1.
- Number of doses received per participant in Cycle 1.
- Total and actual duration of exposure, specific to Cycle 1.
- Number of participants that initiated Cycle 2.

5.6.2 Adverse Events

5.6.2.1 Definitions and Derivations

The MedDRA (version 24.1 at a minimum) will be used to code AEs. AEs will be graded according to the National Cancer institute Common Terminology Criteria for AEs (CTCAE) (using the CTCAE version 5.0).

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

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

- Pre-treatment phase – All AEs with a start date after signing the informed consent form, prior to the first administration of IP that do not subsequently go on to worsen during the treatment emergent phase.
- Treatment emergent phase – All AEs starting or worsening in severity following the first administration of IP for the duration of the treatment period, up to and including 30 days after the last dose of IP as per the study safety follow-up period but prior to subsequent

cancer therapy. AEs with missing start time which occur on the same day as first IP administration will be reported as treatment emergent.

- Post-treatment phase – All AEs starting more than 30 days after last dose of IP or once subsequent cancer therapy is started, whichever is earlier. This period is defined for the purpose of possible causally related SAEs.

Serious Adverse Events (SAEs)

A serious adverse event (SAE) is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the participant
- Is an important medical event that may jeopardize the participant

AEs of special interest

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

The following events will be considered to be AESIs:

- Neutropenia, including Febrile neutropenia, Neutropenic sepsis, neutrophil count decrease
- Thrombocytopenia, including platelet count decrease
- Hepatoxicity, including potential Hy's Law, Drug-induced liver injury, Bilirubin increase with transaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST], or both ALT and AST) increase
- Pyrexia
- TLS
- Myocardial ischaemia

Other categories may be added, or existing terms may be modified as necessary. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which higher-level terms and which preferred terms contribute to each AESI. Further reviews may take place prior to database

lock to ensure any further terms not already included are captured within the categories. Preferred terms used to identify AESIs will be listed prior to database lock.

Other significant adverse events (OAE)

No OAEs are defined for this study.

5.6.2.2 Presentation

All TEAEs will be summarised and listed. AEs which are not treatment emergent will be listed for the Safety set.

TEAEs will be counted once for each participant for calculating percentages of participants experiencing TEAEs. In addition, if the same TEAE occurs multiple times within a particular participant, the highest severity and level of relationship observed will be reported. For tables by MedDRA SOC and MedDRA PT, participants with multiple TEAEs will be counted once for each SOC/PT.

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

Separate tables present AEs leading to discontinuation of IP, IP-related AEs, IP-related AEs leading to discontinuation of IP, AEs leading to dose reduction, AEs leading to dose delay, and AEs leading to dose interruption.

AEs leading to death will also summarised.

SAEs

SAEs will be summarised as described above for the TEAEs.

AEs of special interest

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

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

- At least one AESI presented by event outcome

- At least one AESI causally related to IP
- At least one AESI leading to discontinuation of study intervention.

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

5.6.3 Deaths

5.6.3.1 Presentation

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

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

A corresponding listing will also be produced.

5.6.4 Clinical Laboratory, Blood Sample

5.6.4.1 Definitions and Derivations

Laboratory tests will be grouped according to chemistry, haematology and coagulation. Listings will be provided for all laboratory results. Laboratory parameters will be assessed at baseline as well as throughout the study.

For chemistry and haematology parameters, laboratory abnormalities with toxicity grades according to the NCI CTCAE version 5.0 will be derived.

Laboratory variables that will be measured are detailed in

Table 8 Laboratory Safety Variables

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Table 8 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)		**Clinical Chemistry (serum or plasma)**	
B-Full blood count with differential		S/P-Creatinine	S/P-Chloride
B-Hb		S/P-Bilirubin total	S/P-Magnesium
B-White blood cell count with differential		S/P-Direct and indirect bilirubin (where required)	S/P-Phosphorus
B-Platelet count		S/P-Alkaline phosphatase	S/P-Cholesterol
B-Haemocrit		S/P-Aspartate transaminase	S/P-Amylase
B-Absolute neutrophil count		S/P-Alanine transaminase	S/P-Lactate dehydrogenase
B-Absolute lymphocyte count		S/P-Albumin	S/P-Lipase
B-Blast Cells		S/P-Potassium	S/P-Bicarbonate
Urinalysis (dipstick)		S/P-Carbonate	S/P-glutamate dehydrogenase
U-Hb/Erythrocytes/Blood	U-pH	S/P-Calcium, total	S/P-Blood urea nitrogen
U-Protein/Albumin	U-Bilirubin	S/P-Sodium	S/P-Glucose (fasting preferred)
U-Glucose	U-Ketones	S/P-Creatine phosphokinase	S/P-Total protein
U-Specific gravity	U-Drug screening[a]	S/P-Uric acid	S/P-GGT
U-Microscopy including white blood cells /high-power field, red blood cells/high-power field		S/P-Triglycerides	S/P-Ferritin
Coagulation		S/P-C-reactive protein	S/P-Urea
International normalised ratio		S/P-Troponin	S/P-Phosphate
Activated partial thromboplastin time, absolute or relative		S/P-Ammonia (where available at local institution; to be tested every 2 weeks)	
Prothrombin time			
Fibrinogen			
D-Dimer (where available at local institution)			
Pregnancy Test (women of childbearing potential only)			
U-hCG		S-beta hCG (at screening only)	

[a] Mandated at screening visit only; for all other urinalysis tests, drug screening may be performed at investigator discretion.

Abbreviations: B, blood; GGT, gamma-glutamyl transferase; Hb, haemoglobin; hCG, human chorionic gonadotropin; P, plasma; S, serum; U, urinalysis.

Change from baseline in haematology, clinical chemistry and coagulation endpoints will be calculated for each post-baseline timepoint. CTCAE grade is calculated at each timepoint for

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

Liver Function Parameters

Participants with elevated post-baseline ALT, AST, or Total Bilirubin will be identified.

5.6.4.2 Presentations

The absolute values and change in each laboratory parameter from baseline to each post-baseline timepoint will be summarised graphically in box plots.

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

Listings will be provided for all laboratory results.

Liver Function Parameters

Number and percentage of participants with elevated post-baseline ALT, AST, or Total Bilirubin will be tabulated.

For participants with “Potential Hy’s law”, the change in the following laboratory parameters from baseline to each post-baseline timepoint will be summarised: ALT, AST, alkaline phosphatase, glutamate dehydrogenase, lactate dehydrogenase, gamma-glutamyl transferase, and international normalised ratio. Individual participant data for these laboratory parameters will be listed as well.

Plots for both maximum on-treatment ALT and AST versus the maximum on-treatment bilirubin (expressed as multiples of their upper limit of normal [ULN] reference range) will be produced, with reference lines at 3 x ULN for ALT and AST and 2 x ULN for total bilirubin.

Liver biochemistry test results over time for participants with elevated ALT or AST (≥ 3 x ULN) and elevated bilirubin (≥ 2 x ULN) regardless of whether or not these elevations coincide, or ALT or AST ≥ 5 x ULN will be plotted.

5.6.5 Clinical Laboratory, Urinalysis

5.6.5.1 Definitions and Derivations

Urinalysis variables that will be measured are detailed in

Table 8 Laboratory Safety Variables

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5.6.5.2 Presentations

Shift tables (“Negative”, “Trace”, “Positive”, “0”, “+”, “++”, “+++”) from baseline to worst on-treatment results will be produced for urinalysis.

Listings will be provided for all laboratory results including urinalysis.

5.6.6 Vital Signs

5.6.6.1 Definitions and Derivations

Temperature, blood pressure and heart rate will be assessed.

5.6.6.2 Presentations

Vital signs will be assessed at baseline and throughout the study. Vital signs will be summarised by study timepoint including descriptive statistics for the value of the parameters and the changes from baseline.

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

5.6.7 Weight

5.6.7.1 Presentations

Weight will be assessed at baseline and throughout the study. Weight will be summarised by study timepoint including descriptive statistics for the value and changes from baseline.

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

5.6.8 B symptoms

5.6.8.1 Presentations

Information on B symptoms (unintentional weight loss, disease related intermittent fevers >38 C, drenching sweats especially at night, significant fatigue, worsening of B-symptoms compared to baseline, worsening of B-symptoms compared to prior timepoint, and comments) will be listed for all subjects and timepoints.

5.6.9 Tumour lysis syndrome

5.6.9.1 Definitions and Derivations

Tumour lysis syndrome (TLS) is an important identified risk for AZD4573. TLS prophylaxis is mandatory for all participants starting 3 days before the first dose of AZD4573, which should be followed in addition to institutional guidelines.

There are 2 data sources to report TLS: AEs of TLS and TLS monitoring data. One TLS AE per infusion per participant will be counted. For participants with multiple TLS AEs recorded after one infusion, only the TLS AE with maximum CTCAE grade will be counted for reporting purposes. Similar rules apply to TLS monitoring data. According to the TLS monitoring schedule in the CSP, participants could have multiple TLS monitoring episodes after one infusion, if counting TLS monitoring assessments at each unique date and time per participant as an episode. For reporting purposes, a maximum of one TLS per infusion per participant will be counted. The highest Cairo-Bishop grade of each clinical characteristic (creatinine abnormality, cardiac arrythmia, seizure) and overall grading will be computed for each infusion and participant.

Overall Cairo-Bishop grading for Clinical TLS is defined as the maximum overall on treatment Cairo-Bishop grading, derived from the highest contributing grade (creatinine abnormality, cardiac arrythmia, seizure) for a specific episode of clinical TLS.

5.6.9.2 Presentations

The number and percentage of participants with AE LLTs involving clinical TLS and laboratory TLS by maximum CTCAE grade will be presented, including the total number of AEs. Figures for laboratory TLS and clinical TLS will be presented. Bar charts showing the number of TLS AEs and the number and percentage of participants having TLS AEs by week since AZD4573 administration will be presented. TLS-associated AEs will be listed with other AEs.

Time from infusion to onset of TLS after first AZD4573 administration and after subsequent doses will be summarised using TLS monitoring data. Listing of TLS monitoring will be presented including uric acid, potassium, phosphate, calcium, urea nitrogen, creatinine, creatinine elevation due to TLS, cardiac arrhythmia due to TLS, seizure due to TLS and Cairo-Bishop grades for clinical TLS.

5.6.10 Electrocardiogram

5.6.10.1 Definitions and Derivations

Electrocardiogram (ECG) parameters will be assessed at baseline as well as throughout the study. ECG parameters include PR, RR, QRS, QT, QTcB, and QTcF. The QTcF is considered as the primary correction method to assess participant cardiac safety.

From these resting 12-lead ECGs values of the QT and RR intervals the QTcF and QTcB will be derived using the following formulae:

QTcF = QT/RR^ (1/3) where RR is in seconds

QTcB = QT/RR^ (1/2) where RR is in seconds

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

The notable ECG interval values while on intervention are:

- Maximum QTcF and QTcB intervals > 470 milliseconds, > 480 milliseconds, and > 500 milliseconds.
- Maximum changes from baseline in QTcF and QTcB > 30, >60, and > 90 milliseconds.

5.6.10.2 Presentations

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

The number and percentage of participants having notable ECG interval values on intervention will be summarised.

5.6.11 Echocardiogram

5.6.11.1 Presentations

Left ventricular ejection fraction results will be presented in listings.

5.6.12 Other Safety Assessments

5.6.12.1 Presentations

Serum immunoglobulins (IgA, IgM, IgG) will be listed and summarised descriptively. Absolute values and change from baseline values at each timepoint will be presented.

6 INTERIM ANALYSIS

There will be no interim analysis for Module 1.

7 REFERENCES

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8 APPENDICES

Appendix A Time windows for Module 1 – Efficacy assessments

Timepoint	Tumour assessments
After 8 weeks [a]	49 – 63
After 17 weeks	112 – 126
After 26 weeks	175 – 189

[a] Participants who progress before the "After 8 weeks" timepoint should have had a tumour assessment performed at the time of progression. This tumour assessment will be used for the "After 8 weeks" timepoint.

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