Parexel International

AstraZeneca

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A Modular Phase I/II, Open-label, Multicentre Study to Assess AZD4573 in Novel Combinations with Anti-cancer Agents in Patients with Advanced Haematological Malignancies

Statistical Analysis Plan

Module 1 and Module 2

Version: 5.0

Parexel Project Number: 248067

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LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
AUC(0-inf)	AUC from time zero extrapolated to infinity
AUC(0-t)	AUC from time zero to the last quantifiable concentration
AUClast	Area under the plasma concentration-curve from zero to the last quantifiable concentration
BICR	Blinded independent central review
BID	Twice daily
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
BoR	Best Overall Response
BP	Blood pressure
bpm	Beats per minute
COO	Cell of origin
CR	Complete response
CRF	Case report form
CTC	Common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
Cmax	Maximum observed concentration
CMV	Active Cytomegalovirus
CV	Coefficient of variation
DBP	Diastolic blood pressure
DLBCL	Diffuse large B-cell lymphoma

Abbreviation / Acronym	Definition / Expansion
DLT	Dose-limiting toxicity
DoR	Duration of response
DU	Dose is unsafe
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Co-operative Oncology Group performance status
eCRF	Electronic Case Report Form
FAS	Full analysis set
Gmean	Geometric mean
IHC	Immunohistochemistry
IP	Investigational Product
IPI score	International Prognosis Index score
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MZL	Marginal zone lymphoma
mTPI-2	Modified toxicity probability interval
MUGA	Multi-gated acquisition scan
NA	Not available
NCS	Not clinically significant
NK	Natural killer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PD	Progressive Disease

Abbreviation / Acronym	Definition / Expansion
PET-CT	Positron-emission tomography-computed tomography
PFS	Progression-free survival
PHL	Potential Hy's law
PK	Pharmacokinetics
PKS	Pharmacokinetic analysis set
PR	Partial response / Partial remission
PT	Preferred term
QT	The QT interval is measured from the beginning of the QRS complex to the end of the T wave
QTc	Corrected QT interval
QTcF	QT corrected using Fridericia's formula
RP2D	Recommended Phase II dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
Std Dev	Standard deviation or single dose
SFU	Safety follow-up
SoA	Schedule of Activities
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment emergent adverse event
TLS	Tumour lysis syndrome
TTR	Time to response
ULN	Upper limit of normal
tmax,ss	Time corresponding to occurrence of Cmax,ss at steady state
Vz/F	Apparent volume of distribution during terminal phase
WHODRUG	World Health Organisation Drug Dictionary
λz	Terminal elimination rate constant

Abbreviation / Acronym	Definition / Expansion
λz,ss	Terminal elimination rate constant at steady state

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	09 Aug 2021	New document
2.0	26 Apr 2022	• Updated to be aligned with CSP Amendment v3.0 • Updated to have abbreviations to be defined at first use • Updated Section 1 (Introduction) to remove text about the use of subjects in the document • Updated Section 2.1.2 to remove footnote referring to [a] as there is not superscript in the table • Updated Section 3.2 to add reference note in table footnote • Updated Section 3.3.1 to clarify that part of the text refer to Part A and Part B • Updated Section 3.3.2 as per Labcorp comments Clarified that Pk parameters are for AZD4573, acalabrutinib and its metabolites. AUCextr added to the list of diagnostic parameters for plasma PK • Updated Section 4.2 to remove text to align more to the latest SAP template guidance and to add visit naming conventions for efficacy and non-efficacy data. SD abbreviation changed to Std Dev, where applicable • Updated Section 4.3.2 to add a bullet for dose delays • Updated Section 4.3.3.1 to add a bullet for missing diagnostic dates, flags and end date imputations to take DCO dates into account. • Updated Section 4.5-Table 2 updated DLT-evaluable analysis set definition. Tumour response analysis set changed with Response evaluable set. This update was performed across the document as appropriate. • Updated Section 4.6.1 (disposition of subjects): To add screen failures To remove completed subjects summaries and listings and to add summary for subjects who terminated study To add listings and summaries on subjects impacted with the COVID-19 pandemic • Updated Section 4.7 (demographics and baseline characteristics) to change age group and to add listings

Version No.	Effective Date	Summary of Change(s)
		and summaries on subjects impacted with the COVID-19 pandemic. Reference to subject recycle process document added. • Updated Section 4.8 to remove disease related and relevant terms and to add listings and summaries on subjects impacted with the COVID-19 pandemic • Updated Section 4.9 to change regimens with lines of therapy • Updated Section 4.10 [CR and PR] changed with [CR or PR • Updated Section 4.10.3.1 to add 80% CI for CR rate • Updated Section 4.10.3.2 -Table 4 to add censoring rule for sensitivity analysis • Updated Section 4.10.3.3 to add 80% CI for DoR Supportive analysis added • Updated Section 4.10.3.4 to change "The percentage of subjects…" text with "The proportion of subjects…" • Updated Section 4.10.3.5 to move "supportive data; change in target lesion tumour size" to this section and to add target lesion tumour size definition • Updated Section 4.11.1 to be aligned with current AZ-SAP template Exposure section updated using exposure definition from AZ-Oncology template v0.6 (wording simplified) and adding swimmer plots • Updated Section 4.11.4 to update MedDRA version • Updated Section 4.10.3 to remove table 4 and to use same format/order the CSP has it • Updated Section 4.11.13 • Updated Section 4.14 to add clarifications to CSP • Updated Appendices to remove SoA and Lab. table
3.0	11-Jul-22	• Updated Section 4.2 to add additional summaries • Updated Section 4.5 to update response evaluable analysis set and full analysis set definition and to add modified response evaluable analysis set definition. • Updated Section 4.5 to update response evaluable analysis set definition

Version No.	Effective Date	Summary of Change(s)
4.0	11-Oct-2023	• Updated Introduction to specify the purpose of the additional analysis described in the document (conferences, publications). • Updated Section 2.1 to remove footnote referring to BICR. • Updated Section 2.1.2 to remove abbreviation for pharmacodynamics as per CSP v4.0 • Updated Section 3.2 to align the definition of the primary analysis to CSP v4.0 • Updated Section 3.2 to update the requirements and timing for the interim analysis. • Update Section 3.3.3 to add physical examination to the list of safety and tolerability variables as per CSP. • Updated Section 4.1.4 to remove clarification text regarding discrepancies in the definition of efficacy analysis set(s) with previous version of the CSP. • Updated Section 4.1.4 to clarify discrepancy with CSP v4.0 regarding dose delays for acalabrutinib • Updated Section 4.2 to add details regarding the presentation of the data for the supportive analysis. • Updated Section 4.5 to align the definition of DLT set as per CSP v 4.0. • Updated Section 4.6.1 to describe the listing of subject populations as a supportive analysis. • Updated Section 4.9 to remove the summary of regimens of previous chemotherapies. • Updated Section 4.10 to update Initial disease assessment for DLBCL method from Lugano to Ann Arbor classification as per CSP v4.0. • Updated Section 4.10.3 to add the description of the supportive efficacy analysis performed for conferences and publications • Updated Section 4.10.3.3 to rephrase swimmer plot description. • Updated Section 4.11.1 to remove Dose Delays definition and presentation from acalabrutinib subsection and add under AZD4573. • Updated Section 4.11.6 to update list of clinical chemistry parameters as per CSP v4.0

Version No.	Effective Date	Summary of Change(s)
		• Updated Section 14.11.12 to add CSPv4.0 to the TLS table. • Updated Section 4.12 to update the requirements and timing for the interim analysis • Updated Section 4.12 to update the Analysis set for IA from Response evaluable set to Modified Response evaluable set. • Updated Introduction to describe the purpose of Module 2 and update CSP version. • Updated Section 2.1 to add Module 2 Objectives. • Updated Section 2.1 to update list efficacy endpoints for Module 2 as per defined scope (DoR, PFS and OS). • Updated Section 3.2 to remove interim analysis and add primary analysis for Module 2. • Updated Section 3.3.1 to rephrase the general definition of the efficacy endpoints as per CSP version 5.0 • Updated Section 3.3.1 to add definition of efficacy endpoints for Module 2. • Updated Section 3.3.3 to add the list of Safety and Tolerability variables for Module 2. • Updated Section 4.2 to align the description of the results presentation to the current structure of outputs. • Updated Section 4.5 to update the definition of DLT-evaluable as per CSP version 5.0. • Updated Section 4.5 to add Interim response evaluable set as per CSP version 5.0. • Updated Section 4.10.3 to define the handling of missing post-baseline target lesion measurements. • Updated Section 4.10.3 to remove sensitivity analysis for PFS and OS. • Updated Section 4.11 to specify that safety data for Module 2 subjects will be only listed and no summary tables will be provided. • Updated Section 4.11.2 to define the rules for the derivation of actual dose of AZD4573 in mg. • Updated Section 4.11.2 to add note regarding the protocol allowed window of 2 days for the calculation of cumulative planned dose.

Version No.	Effective Date	Summary of Change(s)
		• Updated Section 4.11.2 to specify that the RDI will not be calculated for Module 2 subjects. • Updated Section 14.11.12 to describe the presentation of TLS laboratory data in Module 1. • Updated Section 4.12 to remove the presentation of the interim analysis and specify the reason as per CSP version 5.0. • Add decimal rules for data recorded in EDC • Populations for tables: No population header or flag for Disposition table, FAS population for important protocol deviations, prior/concomitant medication, and medical history • For OAE, per sponsor add sentence saying data will not be presented. • Updated Section 2.1 to remove Part B to Module 2. Reversed Module 1 Part A and B to show Module 1 first. • Updated Section 2.1.1 to show Module 1 first followed by part. • Updated Section 2.1.2 to show Module 1 first followed by part. • Updated Section 4.2 to align with sponsor reporting standards. • Updated Section 4.11.6. • Updated Section 4.11.7. • Added Section 4.11.14. • Updated Section 4.13 per CSP version 5.0

Version No.	Effective Date	Summary of Change(s)
5.0	27-Oct-2023	• Updated Section 4.5 to revert the DTL population to match SAP V3 and to define backfill subjects.

1 INTRODUCTION

This is a modular, Phase I/II, open-label, multicentre study of AZD4573 administered intravenously in novel combinations with other anti-cancer agents, to subjects with advanced haematological malignancies.

Module 1 will be investigating AZD4573+acalabrutinib in subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) or relapsed or refractory marginal zone lymphoma (MZL).

Module 2 will be investigating 2 cycles (8 weeks) AZD4573 monotherapy (Period 1) followed by AZD4573 + acalabrutinib combination treatment (Period 2) in subjects with relapsed or refractory (r/r) Mantle Cell Lymphoma (MCL).

The statistical analysis plan (SAP) provides a technical elaboration of the statistical analysis to be performed for Module 1 and Module 2 as outlined in the clinical study protocol (CSP). Details provided in this document will also support the statistical analysis for conferences and publications.

The analyses described in this SAP are based upon the following study document:

- Study Protocol, Version 5.0 (June 01, 2023)

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

2 STUDY OBJECTIVES

2.1 Primary Objectives

Objectives	Endpoints/Variables
Module 1 – Part A	
• Assess the safety and tolerability, describe the DLTs, and identify the MTD and/or RP2D of AZD4573 in combination with acalabrutinib (100 mg BID).	• Adverse events, DLTs, laboratory data, vital signs, and ECG changes.
Module 1 – Part B	
• Assess the efficacy of AZD4573 in combination with acalabrutinib by evaluation of objective response rate.	• Endpoint based on revised response criteria for malignant lymphoma (Cheson et al 2014): ○ ORR, defined as the proportion of subjects who have a tumour response (CR or PR) a

Abbreviations: BID = twice daily; CR = Complete response; DLT = dose-limiting toxicity; ECG = electrocardiogram; MTD = maximum tolerated dose; ORR = Objective response rate; PR = Partial response; RP2D = recommended Phase II dose.

Objectives	Endpoints/Variables
Module 2	
• Assess the safety and tolerability of the RP2D of AZD4573 in combination with acalabrutinib (100 mg BID) for subjects	• Adverse events (including SAEs), dose modifications, treatment discontinuation due to AE, AESIs, laboratory data, vital signs, and ECG changes.

Objectives	Endpoints/Variables
who are administered AZD4573 monotherapy.	
• Assess the safety and tolerability and confirm the RP2D of AZD4573 monotherapy in MCL.	• Adverse events (including SAEs), dose modifications, treatment discontinuation due to AE, AESIs, laboratory data, vital signs, and ECG changes.

Abbreviations: BID = twice daily; ECG = electrocardiogram; RP2D = recommended Phase II dose; SAE=Serious Adverse Event, AESI=Adverse Event of Special Interest; MCL= mantle cell lymphoma.

2.1.1 Secondary Objectives

Objectives	Endpoints/Variables
Module 1 – Part B	
• Assess efficacy of AZD4573 in combination with acalabrutinib by evaluation of tumour response and overall survival	• Endpoints based on revised response criteria for malignant lymphoma (Cheson et al 2014): – CR rate – DoR – TTR – PFS • OS
• Assess the safety and tolerability of the RP2D of AZD4573 in combination with acalabrutinib (100 mg BID)	• Adverse events, laboratory data, vital signs, and ECG changes
Module 1 – Part A and B	
• Assess the plasma PK of AZD4573 and acalabrutinib (plus its active metabolite ACP-5862), when given in combination.	• Plasma concentrations and derived PK parameters for AZD4573 summarised by cohort and dose level for the PK analysis set • Plasma concentrations and derived PK parameters for acalabrutinib and its metabolite ACP-5862 summarised by cohort and dose level for the PK analysis set

Abbreviations: BID = twice daily; CR = Complete response; DoR = duration of response; ECG = electrocardiogram; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RP2D = recommended Phase II dose; TTR = time to response.

Objectives	Endpoints/Variables
Module 2	
• Assess the plasma PK of AZD4573 (when given alone and in combination with acalabrutinib 100 mg) and acalabrutinib	• Plasma concentrations and derived PK parameters for AZD4573 for the PK analysis set. • Plasma concentrations and derived PK parameters

Objectives	Endpoints/Variables
(plus its active metabolite ACP-5862).	for acalabrutinib and its metabolite ACP-5862 for the PK analysis set.

Abbreviations: PK = pharmacokinetics.

2.1.2 Exploratory Objective(s)

Objectives	Endpoints/Variables
Module 1 – Part A	
• Assess efficacy of AZD4573 in combination with acalabrutinib by evaluation of objective response rate, tumour response, and overall survival.	• Endpoints based on revised response criteria for malignant lymphoma (Cheson et al 2014): – ORR – CR rate – DoR – TTR – PFS • OS
Module 1 – Part A and B	
• Assess the pharmacodynamics of CCI [redacted]	• CCI [redacted]
• Assess CCI [redacted]	• CCI [redacted]
• To evaluate CCI [redacted]	• CCI [redacted]
• To CCI [redacted]	• CCI [redacted]

Abbreviations: BID = twice daily; CCI [redacted]

Objectives	Endpoints/Variables
Module 2	
• Explore activity of AZD4573 alone, and in combination with acalabrutinib by evaluation of tumour responses and overall survival.	• Endpoints based on revised response criteria for malignant lymphoma (Cheson et al 2014): – DoR – PFS • OS
• Assess CCI [redacted]	• CCI [redacted]
• Assess CCI [redacted]	• CCI [redacted]
• To CCI [redacted]	• CCI [redacted]

CCI [redacted] DoR = duration of response; CCI [redacted] OS = overall survival; CCI [redacted] PFS = progression-free survival; CCI [redacted]

Exploratory endpoints related to the pharmacodynamics of AZD4573 and acalabrutinib, CCI [redacted] may be reported outside of the CSR and will not be described further within this SAP.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

Refer to Section 13.1 for Module 1 and Section 22.1 for Module 2 of the CSP.

3.2 Planned Analyses

The details of the analyses planned during the conduct of this study is outlined in Table 1.

Table 1 Summary of Analyses During Study Conduct

Analysis	Trigger
Primary Analysis Module 1	The data cut-off (DCO) for the primary analysis for each expansion subgroup will occur approximately 6 months following last subject first dose in the expansion subgroup or when 75% of subjects have progressed or died in the cohort, whichever occurs first.
Primary Analysis Module 2	The data cut-off for the primary analysis of Module 2 will occur approximately 6 months following last-subject first-dose of AZD4573 monotherapy or when 75% of subjects have progressed or died in Module 2, whichever occurs first. All available data from Period 1 (AZD4573 monotherapy) and Period 2 (AZD4573 plus acalabrutinib) will be analysed.
Final Analysis[A]	At the end of each module a final analysis will be conducted to incorporate all data (up to and beyond the primary analysis) from all subjects.

[A] Refer to subject recycling process document in appendix for details.

If the sponsor decides to terminate the study early, the primary analysis of each module is considered final analysis.

3.3 Endpoints and Associated Variables

3.3.1 Efficacy Variables

Module 1 – Part B

The primary objective is to assess the efficacy of AZD4573 in combination with acalabrutinib by evaluation of objective response rate (ORR) per the Lugano classification for Non-Hodgkin Lymphoma (NHL) (Cheson et al 2014) (hereafter referred to as Lugano classification) as assessed by investigators.

The secondary objectives are to:

Assess the efficacy of AZD4573 in combination with acalabrutinib by evaluation of tumour response.

- Complete response (CR) rate per Lugano classification as assessed by investigators
- Duration of response (DoR) per Lugano classification as assessed by investigators
- Time to response (TTR) per Lugano classification as assessed by investigators
- Progression-free survival (PFS) per Lugano classification as assessed by investigators
- Overall survival (OS)

Module 1 – Part A

The exploratory objective is to assess the efficacy of AZD4573 in combination with acalabrutinib by evaluation of:

- ORR per Lugano classification as assessed by investigators
- CR rate per Lugano classification as assessed by investigators
- DoR per Lugano classification as assessed by investigators
- TTR per Lugano classification as assessed by investigators
- PFS per Lugano classification as assessed by investigators
- OS

Module 1 – Part A and B

The efficacy variables, all per the Lugano classification as assessed by investigators (Cheson et al 2014), are defined as follows:

- ORR is defined as the proportion of subjects who achieve either a PR or CR.
- CR rate is defined as the percentage of subjects who achieve a CR.
- DoR defined as the time from the first documented objective response to the time of documented disease progression or death due to any cause, whichever occurs first.
- TTR is defined as time from the first dose of study treatment to the first documented objective response observed for subjects who achieved a CR or PR.
- PFS is defined as time from date of first dose to documented disease progression, or death from any cause, whichever occurs first.
- OS is defined as the time from date of first dose until the date of death from any cause.

Module 2

An exploratory objective is to explore activity of AZD4573 alone, and in combination with acalabrutinib, by evaluation of tumour responses and overall response per revised response criteria for malignant lymphoma (Cheson et al 2014). The following efficacy endpoints will be analysed: Duration of response (DoR), Progression-free survival (PFS) and Overall survival (OS).

3.3.2 Pharmacokinetic Variables

Pharmacokinetics analysis is a secondary objective for both Module 1 (Part A and Part B) and Module 2. PK parameters for AZD4573, acalabrutinib and its metabolite ACP-5862 will be calculated by non-compartmental analysis methods using Phoenix® WinNonlin® (Version 8.1) or higher as data applicable.

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

PK analysis will, where data allow, be carried out using actual elapsed times determined from the PK sampling and dosing times recorded 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.

For AZD4573 (IV infusion), the following PK parameters will be calculated using the PK concertation vs time data from Cycle 1 Day1 of Week 1-3, and Cycle 2 Day 1, as data applicable.

Cmax	Maximum observed plasma (peak) drug concentration
tmax	Time to reach peak or maximum observed concentration following drug administration
λz	Terminal elimination 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 time 0 to time 24 hours
AUClast	Area under the plasma concentration-curve from zero to the 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
Vd	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-normalized Cmax
AUClast/D	Dose-normalized AUClast
AUCinf/D	Dose-normalized AUCinf

Additional PK parameters may be determined where appropriate.

For acalabrutinib and ACP-5862, the following PK parameters will be calculated using the PK concentration vs time data from Cycle 1 Day 1 of Week 1, as data applicable.

Cmax	Maximum observed plasma (peak) drug concentration
tmax	Time to reach peak or maximum observed concentration following drug administration
λz	Terminal elimination 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(0-12)	Area under the plasma concentration-time curve from time 0 to time 12 hours
AUClast	Area under the plasma concentration-curve from zero to the last quantifiable concentration
AUCinf	Area under plasma concentration-time curve from zero to infinity
CL/F	Apparent total body clearance of drug from plasma after extravascular administration (parent drug only)
Vz/F	Apparent Volume of distribution following extravascular administration (based on terminal phase) (parent drug only)
MP ratio	Metabolite: parent ratio; AUCinf metabolite/AUCinf parent, Cmax(metabolite)/Cmax(parent) (metabolite only)
tlast	Time of last observed quantifiable concentration

Additional PK parameters may be determined where appropriate.

For acalabrutinib and ACP-5862, the following PK parameters will be calculated using the PK concentration vs time data from Cycle 1 Day 1 of Week 2, 3, and Cycle 2 Day 1, as data applicable.

Cmax	Maximum observed plasma (peak) drug concentration
Tmax	Time to reach peak or maximum observed concentration or response following drug administration during a dosing interval at steady state
AUCτ	Area under plasma concentration-time curve in the dosing interval τ, the τ is 12 hours
CL/F	Apparent total body clearance of drug from plasma after extravascular administration calculated as dose/ AUCτ
AUClast	Area under the plasma concentration-curve from zero to the last quantifiable concentration
Tlast	Time of last observed (quantifiable) concentration
Cmin	Minimum observed plasma drug concentration
Cavg	Average drug concentration during a dosing interval

Additional PK parameters may be determined where appropriate.

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

AUCextr	Extrapolated area under the curve from tlast to infinity (%)
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 ratio of t½λz

The time period used for the estimation of apparent terminal elimination half-lives, where possible, should be over at least two 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 CSR.

3.3.3 Safety and Tolerability Variables

Module 1 – Part A

The primary objective of Part A is to assess the safety and tolerability, describe the DLTs, and identify the MTD and/or RP2D of AZD4573 in combination with acalabrutinib (100mg BID) in subjects with relapsed/refractory DLBCL or MZL.

Data from all cycles of treatment will be combined in the presentation of safety data.

An overall summary table of the number of subjects experiencing each category of adverse events will be produced.

The number of subjects experiencing treatment emergent adverse events by MedDRA system organ class (SOC) and MedDRA preferred term (PT) will be presented, with further splits by CTCAE grade, causal relationship to study medication and adverse events classed as Grade 3 or higher.

Separate tables will present dose limiting toxicities, adverse events leading to discontinuation, serious adverse events (SAES) and other significant adverse events. All AE data will be listed appropriately.

AEs occurring prior to first dose of investigational product (ie, before study Day 1) which subsequently worsen in severity following dosing will be presented in the summary tables. All other AEs occurring prior to first dose of investigational product (ie, before study Day 1), or after the 30-day follow-up period after discontinuation of investigational product will be listed separately, but not included in the summaries.

Module 1 – Part B

The secondary objective of Module 1 Part B is to assess the safety and tolerability of the RP2D of AZD4573 in combination with acalabrutinib (100 mg BID) in subjects with relapsed or refractory DLBCL with GCB or non-GCB subtype.

The following assessments will be performed:

- Adverse event (AE) assessments
- Dose limiting toxicities (DLTs) defined in Section 4.11.3
- Clinical laboratory tests described in Section 4.11.6
- Vital signs (systolic blood pressure [SBP] and diastolic blood pressure [DBP], pulse rate, oral body temperature), height and weight
- 12-lead Electrocardiograms (ECG)
- Tumor lysis syndrome (TLS)
- B symptoms (unintentional weight loss, fevers and night sweats)
- Eastern Cooperative Oncology Group performance status (ECOG PS)
- Left ventricular ejection fraction (echocardiograms [ECHO] / multi-gated acquisition scan [MUGA])
- Physical examinations

The full list of laboratory measurements performed during the study that are used to evaluate safety and tolerability variables can be found in Section 4.11.6.

Module 2

The secondary objective of Module 2 is to assess the safety and tolerability of the RP2D of AZD4573 in combination with acalabrutinib (100 mg BID) in subjects administered AZD4573 monotherapy and to confirm the RP2D of AZD4573 monotherapy in MCL.

The following assessments will be performed:

- Vital signs (blood pressure, pulse rate, temperature)
- 12-lead Electrocardiogram (ECG)
- Clinical laboratory tests (haematology, clinical chemistry, coagulation, urinalysis parameters, CD4, CD8, CD19, CD16/NK, cardiac troponin I or troponin T measurements, electrolyte panel, supra-renal glands and Lipase and amylase measurements)
- Adverse event (AE) assessments
- Dose modifications
- Tumour lysis syndrome (TLS)
- B symptoms (unintentional weight loss, fevers and night sweats)
- Eastern Cooperative Oncology Group performance status (ECOG PS)
- Left ventricular ejection fraction (echocardiograms [ECHO] / multi-gated acquisition scan [MUGA]).

4 STATISTICAL METHODS

4.1 Data Quality Assurance

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

4.2 General Presentation Considerations

The following considerations will be applicable to all modules.

Continuous data will be summarised in terms of the mean, standard deviation (Std Dev), median, 25th and 75th percentiles (where appropriate), minimum, maximum and number of observations. If data are available for less than 3 subjects, no summary statistics other than minimum, maximum and number of observations will be presented. For log--transformed data it is more appropriate to present geometric mean (gmean), geometric coefficient of variation (CV), median, minimum and maximum.

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

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

Confidence intervals (CIs), when presented, will generally be constructed at 2-sided 80% and 95% level. CIs will be presented to one additional place than the original data. When presented, P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

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

For categorical data, percentages will be rounded to 1 decimal place. In Module 1, summary tables will be presented by dose level combining Module 1 Part A and Module 1 Part B subjects unless otherwise stated. Data from RP2D-treated Module 1 Part A subjects that meet entry criteria for Module 1 Part B will also be included in Module 1 Part B.

A subgroup analysis will be performed. For the purposes of recycling of data from Module 1 Part A subjects for analysis with Module 1 Part B subject data, cell of origin (COO data) from local assessment will be used. The histology subtype was assigned by local sites, and it was confirmed by central laboratory only for subset of GCB and non-GCB subjects were treated at RP2D (AZD4573 12 mg) and all Module 1 Part B subjects.

Efficacy endpoints may also be summarised by other relevant subgroups (eg, Lymphoma classification, Histology subtype, prior anti-cancer therapies [CAR-T, BiTE and BTKi]).

Generally, the last observation prior to the first dose of the study treatment, will be considered the baseline measurement. For non-numeric laboratory tests (ie some of the urinalysis parameters) where taking an average is not possible then best value would be taken as baseline as this is the most conservative. In the scenario where there are two assessments on day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline (if it is earlier than the start time of study treatment). Where safety data are summarised over time, study day will be calculated in relation to date of first dose.

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

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

post-baseline value - baseline value

Percent change from baseline will be calculated as:

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

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

Visits 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

All other data will follow the following naming conventions:

- Cycle 1 (ramp-up):
  - Cycle 1 6 mg AZD4573 dose x
  - Cycle 1 9 mg AZD4573 dose x
  - Cycle 1 12 mg AZD4573 dose x
    - "x" is replaced with "1", "2", "3", etc. as applicable, and refers to the count of the dose received at that specified amount.
- Cycle 2 onwards:
  - Cycle 2 Day 1
  - Cycle 2 Day 8
  - Cycle 2 Day 15
  - Cycle 3 Day 1
    - That is, the visit name as per schedule of activities in the CSP is followed.

4.3 General Variables

4.3.1 Study Day Definitions

Study day 1 is defined as the date of first dose of Investigational Product (IP) (Cycle 1 Day 1).

For visits (or events) prior to first dose, study day is defined as (date of visit [event] – date of first dose of IP). For visits (or events) that occur on or after first dose of IP, study day is defined as (date of visit [event] – date of first dose of IP + 1). There is no study day 0.

"Days since last dose" 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. Thus, events on the same day as the last dose will be described as occurring zero days from last dose of IP.

4.3.2 Visit Window

For safety and tumour assessments, visit windows will be defined for any presentations that summarise values by visit. The following conventions will apply:

For tumour assessments:

- The protocol assigned windows for tumour assessments will be used to assign the result to a particular visit.
- For example, the visit windows for tumour assessments are:
    - After 8 weeks: 49-63
    - After 17 weeks: 112-126
    - After 26 weeks: 175-189

For safety assessments:

- The time windows will be exhaustive so that data recorded at any timepoint has the potential to be summarised. Inclusion within the time window will be based on the actual date and not the intended date of the visit.
- All unscheduled visit data will have the potential to be included in the summaries.
- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls halfway between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day.
- For example, the visit window for AZD4573 administration (with 1 week between scheduled visits) are:
    - Cycle 1 6 mg AZD4573 Dose 1:1
    - Cycle 1 9 mg AZD4573 Dose 1: 2-11
    - Cycle 1 12 mg AZD4573 Dose 1: 12-18
    - Cycle 1 12 mg AZD4573 Dose 2: 19-25
    - Cycle 1 12 mg AZD4573 Dose 3: 26-32

- If dose delays are experienced, the planned dosing visit windows will be modified during the programming to anchor to the actual visit date where intervention was administered on to adjust for these dose delays. The same rules apply to safety visits of other types (non-dosing visits) where the safety visit is moved due to a dose delay. For example, if the Day 8 dose is taken on Day 10, the visit windowing will be anchored around Day 10 for this visit.
- Visit windowing will be done separately for each assessment based on the schedule of events specific to that assessment.
- Should Study Day be missing (due to partial or missing dates), then visit will be assigned to the nominal visit at which that assessment was recorded, and no windowing will be performed.
- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment (from the day of the first IP administration up to the day of the last IP administration) will be used (regardless of where it falls in an interval).
- Listings should display all values contributing to a time point for a subject.
- If multiple measurements are taken on the same day, due to inappropriate procedures or any other issues with the first measurement, the reassessment measurement on that day will take preference for analysis, should the values for that day be in the analysis after visit windowing rules have been applied.
- If there are more than one value per subject within a time window then the closest value to the scheduled visit date should be summarised, or the earlier, in the event the values are equidistant from the nominal visit date. The listings should highlight the value for the subject that contributed to the summary table, wherever feasible. Note: in summaries of extreme values all post baseline values collected are used including those collected at unscheduled visits regardless of whether the value is closest to the scheduled visit date.

4.3.3 Handling of Missing Data

In general, other than for the below described, or where otherwise specified in the particular analysis, missing data will not be imputed and will be treated as missing. The imputed dates should not be used to calculate durations, where the results would be less accurate.

4.3.3.1 Imputations of Partial Dates

- 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 concomitant medication and adverse events start dates, the following is applied:
    - Missing day: imputed with the 1st of the month, unless month and year are the same as month and year of first dose of IP, then impute with first dose date.
    - Missing day and month: imputed with the 1st of January unless the year is the same as the year of first dose of IP, then imputed with first dose date.
    - Completely missing: imputed with date of first dose of IP, unless the end date suggests it could have started prior to this in which case it is imputed 1st January of the same year as at the end date.

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

- For missing concomitant medication and adverse events end dates, the following is applied:
  - Missing day: imputed with the last day of the month, unless both the month and year are the same as month and year of last dose of IP, or the primary analysis date cut-off (DCO) date then imputed with the last treatment date in that month or the primary analysis date cut-off (DCO) date.
  - Missing day and month: imputed with the 31st of December unless the year is the same as the year of last dose of IP or the primary analysis DCO date, then imputed with the last treatment date in that year or the primary analysis DCO date.
  - Completely missing: no date imputed (the event is assumed to be ongoing).

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.

4.3.4 Imputation Rules for Laboratory Values Outside of Quantification Range

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

4.4 Software

All report outputs will be produced using SAS® version 9.4 in a secure and validated environment. PK analyses will be produced using Phoenix® WinNonLin (WNL) version 8.1 or later in a secure and validated environment.

4.5 Analysis Sets

Details of the analysis sets are presented in Table 2.

Table 2 Analysis Sets

Analysis Set	Definition
Enrolled	All subjects that signed the informed consent form (ICF).
Safety	All subjects who received any amount of AZD4573 and/or acalabrutinib. For safety analyses subjects will be reported by the actual treatment(s) received and grouped by their assigned target dose level of AZD4573.

Analysis Set	Definition
DLT-evaluable	A DLT-evaluable subject is defined as a subject enrolled in the dose-setting part of the study (Part A) that has received AZD4573 in combination with acalabrutinib and either: • Has received at least 3 doses of AZD4573 at the designated target dose level, has received at least 75% of acalabrutinib doses during the AZD4573 treatment weeks and has completed sufficient safety assessments (as determined by SRC review) through the DLT assessment period. The DLT-assessment period is assumed to have been completed with adequate safety assessments for SRC evaluations if 3 doses of AZD4573 were received at the designated target dose level. In case of an extended DLT period (longer than 5 weeks), where there has been AZD4573 dose interruption(s), the requirement for at least 75% of planned acalabrutinib doses will be applicable only to AZD4573 treatment weeks. If the time period between two consecutive AZD4573 infusion dates does not exceed 9 days, the AZD4573 treatment week is defined as: from the day of AZD4573 infusion until the 9th day or the next AZD4573 infusion, whichever comes first. In case the next AZD4573 dose was administered >= 10 days after the previous AZD4573 dose, the AZD4573 treatment week is defined as: from the day of AZD4573 infusion until the 7th day. Or • Has experienced a DLT during the DLT-assessment period. (For analysis reporting purposes, the DLTs are as approved and documented at the Safety Review Committee meetings.) This excludes a subject that is part of the backfill. If a subject is assigned to Part A in Module 1 and has an ICF signed after CCI (the date of the SRC when RP2D was declared, and decisions were made to open Part B and backfill Part A), then he/she is considered backfill.
Pharmacokinetics (PK)	All dosed subjects with reportable plasma concentration and no important protocol deviations that may impact PK. Subjects will be reported by the actual treatment(s) received and grouped by their assigned target dose level of AZD4573.
Response evaluable	Subjects dosed with AZD4573 or acalabrutinib with measurable disease (longest diameter greater than zero) at baseline.

Analysis Set	Definition
Interim response evaluable	Subjects dosed with AZD4573 or acalabrutinib, or both AZD4573 and acalabrutinib with baseline tumour assessment and have their first post-baseline disease assessment performed or have discontinued study treatment for any reasons before their first post-baseline disease assessment.
Full Analysis Set (ITT)	All subjects who received any amount of AZD4573 and/or acalabrutinib.

Abbreviations: DLT = dose-limiting toxicity; ICF = informed consent form; ITT intention-to-treat; PK=pharmacokinetics.

Upon database release, protocol deviations and analysis set outputs will be produced and will be sent to AZ for review. Prior to database lock for the primary analysis, an analysis set classification meeting will be arranged to discuss the outputs and to decide which subjects and/or subject data will be excluded from certain analyses. Decisions made regarding the exclusion of subjects and/or subject data from analyses will be made prior to primary analysis lock and will be documented and approved by AZ.

A summary on which analysis set will be used for each outcome variable is provided in Table 3.

Table 3 Summary of outcome variables and analysis sets

Outcome Variable	Analysis Set
Study Population/Demography Data	
Disposition	All Subjects
Demography and baseline characteristics	FAS
Important protocol deviations	FAS
Medical History	FAS
Prior/Concomitant Medication	FAS
Safety data	
Exposure	Safety
Adverse Events	Safety
Laboratory measurements	Safety
Vital Signs/ECG/Physical examination	Safety
ECOG PS	Safety
DLTs	DLT evaluable
Efficacy Data	
CR rate	Response evaluable
TTR	Response evaluable
DoR	Response evaluable

Outcome Variable	Analysis Set
PFS	FAS
OS	FAS
ORR	Response evaluable
Pharmacokinetics	
Pharmacokinetic variables	PK

Abbreviations: CRR = Complete response rate; DLT = dose-limiting toxicity; DoR = duration of response; ECOG PS= Eastern Co-operative Oncology Group performance status; FAS = full analysis set; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PK = pharmacokinetic; TTR: = time to objective response.

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

4.6 Study Subjects

4.6.1 Disposition of Subjects

Module 1 – Part A and Part B:

Subject disposition from screening to study completion will be listed and summarised for all subjects. Summaries will include:

- Number of subjects enrolled (informed consent received)
- Number of screen failures (including reasons)
- Number and percentage of subjects who received treatment (including reasons for those that did not receive treatment)
- Number and percentage of subjects ongoing in the study at data cut-off (DCO)
- Number and percentage of subjects ongoing treatment at DCO
- Number and percentage of subjects who discontinued treatment (including reasons for discontinuation)
- Number and percentage of subjects who terminated study

Subject discontinuations will be listed, including dose level/cohort, the date of study exit, total treatment duration (days), actual treatment duration (days) and reason for discontinuation. Total treatment duration and actual treatment duration will be derived as described in Section 4.11.1.

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

- Subjects who discontinue intervention due to COVID-19;
- Subjects who withdrew from study due to COVID-19.

The number and percentages of subjects with confirmed or suspected COVID-19 infection will be presented separately, including details on COVID-19 related interruptions impacting visits and IP administration. Listings of subjects 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.

As supportive analysis, all enrolled subjects will be presented in a listing indicating the different analysis sets in which these are included and flagging all those belonging to the backfill cohorts, this latter category includes all subjects enrolled after SRC CCI

Module 2:

All subjects enrolled in Module 2 will be presented, including the enrollment into Period 1 and Period 2. In addition, subjects who discontinued study and /or affected by Global/country situation will be appropriately listed.

4.6.2 Protocol Deviations

Important protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study intervention. Protocol deviations will be collected and classified as defined in the protocol deviations specification. The final assessment of Protocol Deviations will be performed at a Data Review Meeting (DRM) shortly before database lock. Results and population assignments will be summarized in a DRM report which will be signed off by all relevant scientific experts.

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.

- Subjects 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.
- Subjects deviating from prescribed dosing regimen.
- Missed visits, 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 subject's data, or the subject's rights, safety or wellbeing.
- Missing scheduled efficacy assessments
- Deviation from Good Clinical Practice as determined by medical review (for example insufficient informed consent)

The important protocol deviations affecting Module 1 subjects will be listed and summarised by dose level on the Full Analysis Set. Important protocol deviations related to COVID-19 will be summarised separately.

The important protocol deviations affecting Module 2 subjects will be only presented in a listing.

A full list of protocol deviations can be found in the study-specific Protocol Deviation Specification. Protocol deviations will be reviewed on a regular basis between AZ and Parexel Data Operations.

4.7 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarised and listed for all subjects in the Safety Analysis Set by dose level/cohort:

- Demographic characteristics (age[years], age group [(≥18 - 64, ≥65 - 74, ≥75 - 84, ≥85)], sex [female; male], race, ethnicity and country).
- Subject characteristics at baseline (height[cm], weight [kg], and body mass index [BMI] [kg/m2]).
- Previous disease related treatment modalities by preferred group.
- Any other subject/disease characteristics at baseline as specified below.

Subject/disease characteristics at baseline:

- Eastern Cooperative Oncology Group (ECOG) performance status
- Histology type
- Lymphoma classification
- Lugano Modification of Ann Arbor Staging
- International Prognosis Index (IPI) score
- Brain involvement
- Spleen involvement
- Bone marrow involvement
- Liver involvement
- Extranodal involvement
- Bulky nodal disease
- Histology subtype /cell of origin (COO)

The histology subtype will be assigned by local sites for Module 1 Part A GCB and non-GCB subjects who are treated at RP2D (refer to the subject recycling process document) and all Module 1 Part B subjects.

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

4.8 Medical/Surgical History

Medical history and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 (as a minimum). Disease related medical history will be listed and the number and percentage of subjects with any disease related medical history will be summarised for

the Safety Analysis Set by system organ class (SOC) and preferred term (PT), by dose level/cohort and overall.

Surgical history will be listed and summarised similarly.

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

4.9 Concomitant Medications and Other Treatments

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

For inclusion in prior and/or concomitant medication or therapy summaries, incomplete medication or radiotherapy start and stop dates will be imputed as detailed in Section 4.3.2.

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

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

All concomitant medication will be listed by subject and will include the reported name, PT, ATC, route of administration, dose, frequency, start date/time, duration and indication and will be summarised by ATC and PT, dose level/cohort.

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

The following summaries will be produced:

- Previous cancer therapies
- Lines of previous cancer therapies
- Previous chemotherapy
- All concomitant medications

Post-discontinuation cancer therapies will be listed.

All prior, concomitant and post IP medication data (including surgical procedures) will be listed.

Missing coding terms (ATC or Preferred term [PT]) will be listed and summarised as uncoded terms.

All listings and tables will be based on the Safety Analysis Set.

4.10 Efficacy Evaluation

Module 1:

Module 1 Parts A and B include the following efficacy endpoints: objective response rate (defined as the proportion of subjects who have a tumour response [CR or PR] by investigator assessment), CR rate, TTR, DoR, PFS and OS.

All assessments of anti-tumour activity will be done by the investigators using standard response criteria as specified in Section 17.4 of the CSP.

Initial disease assessment for DLBCL include staging by Ann Arbor classification.

Tumour assessments will be made for measurable disease, non-measurable disease, and new lesions on CT and combined with visual assessment of PET-CT for response assessment according to the revised response criteria for malignant lymphoma (refer to Table 17 of CSP).

All response assessments will be made by the investigator. All images for the assessment of response will be collected and stored for potential central review. Additional disease assessments may be performed as clinically indicated.

The following tumour assessment details will be listed by subject:

- Target lesion size
- Non-target lesion
- New lesion
- Spleen/Liver Disease

Module 2:

For Module 2 subjects, all figures and listings will be based on the FAS or Safety analysis sets, except the Response assessment figure that will be based on the Response Evaluable set. Data will appropriately be listed by treatment period.

4.10.1 Analysis and Data Conventions

No hypotheses are planned to be tested.

4.10.1.1 Multi-centre Studies

No adjustments for center will be performed.

4.10.1.2 Adjustments for Covariates

No adjustments for covariates will be performed.

4.10.1.3 Handling of Dropouts or Missing Data

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

4.10.2 Primary Efficacy Endpoint

In Module 1 Part B, the primary efficacy endpoint is the objective response rate (ORR). Primary efficacy endpoint will be analysed and presented by dose level.

4.10.2.1 Objective response rate (ORR)

The ORR is defined as the proportion of subjects 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, all subjects who received any amount of AZD4573 and acalabrutinib with measurable disease at baseline. 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 subject withdraws from therapy. Subjects who discontinue study treatment 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 visit contributing to a response must be prior to subsequent therapy for the subject to be considered as a responder).

The ORR will be based on the investigator Lugano data and using all scans regardless of whether they were scheduled or not.

Summaries will be produced that present the number and percentage of subjects with a tumour response (CR or PR) based upon the number of subjects with measurable disease at baseline per investigator. ORR will be calculated and binomial exact 2-sided confidence intervals (CIs) at 80% and 95% will be presented for subjects in the Response Evaluable Set.

Best overall response (BoR)

BoR is calculated based on the overall visit responses from Lugano assessments by the investigator recorded in the eCRF. It is the best overall response a subject has had following start of study treatment, but prior to starting any subsequent cancer therapy and up to and including Lugano progression or the latest evaluable assessment in the absence of Lugano progression. Categories of BoR will be based on Lugano criteria using the following response categories (CR, PR, SD, PD and NE).

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

4.10.3 Other Efficacy Variables

In Module 1 Part A and Module 2, all efficacy endpoints are exploratory. In Module 1 Part B, all efficacy endpoints other than ORR are secondary.

All listings and summaries will be based on the Response Evaluable Set, except PFS and OS that will be based on the FAS as defined in Table 3.

Tumour response data will be listed and summarised by dose level, if appropriate, using the Lugano Response Criteria for Non-Hodgkin's Lymphoma in Table 17 of the CSP.

4.10.3.1 Complete Response (CR) Rate

CR is defined as the proportion of subjects who achieve CR, according to the response criteria for malignant lymphoma reported by the investigator (Cheson et al 2014). CR Rate will be calculated and binomial exact 2-sided CIs at 80% and 95% will be presented for subjects in the Response Evaluable Set.

4.10.3.2 Time to Response (TTR)

Time to response (TTR) is defined as the time from the first dose of study treatment to the first documented objective response. TTR data will be listed and summarised in subjects who achieved an objective response. TTR (months) = (date of first objective response – date of first dose + 1) / (365.25/12).

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

Subjects who discontinue study treatment without a response or progression, receive a subsequent anti-cancer therapy, and then respond will not be included (ie, the visit contributing to a response must be prior to subsequent therapy for the subject to be considered as a responder).

If numbers of responders allow, the median TTR and two-sided 95% CI will be assessed using the Kaplan-Meier method (without censoring because all subjects have events). The number of subjects with response at different disease assessment timepoints may be provided.

4.10.3.3 Duration of Response (DoR)

DoR is defined as the time from the first objective response to the time of documented disease progression or death due to any cause, whichever occurs first.

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

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

Individual duration of treatment and duration of response will be appropriately presented in a swimmer plot (including non-responders subjects) and all response assessments performed by the investigator will be displayed.

Only subjects who have achieved objective response (CR or PR) are included in the summaries of DoR. If numbers 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.

4.10.3.4 Progression-free Survival (PFS)

Disease progression will be determined by the investigators according to the revised response criteria for malignant lymphoma (Cheson et al 2014).

PFS is defined as the time from first dose date to documented disease progression, or death (from any cause in the absence of progression), regardless of whether the subject withdraws from therapy or receives another anti-cancer therapy prior to progression.

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

Subjects who are progression free and alive at the time of data cut-off, or have unknown status, will be censored at the time of the latest date of assessment from their last evaluable disease assessment. However, if the subject progresses or dies immediately after two or more consecutive missed visits, the subject is censored at the time of the latest evaluable disease assessment prior to the two missed visits. Note: a NE visit is not considered as a missed visit.

Given the scheduled visit assessment scheme (ie, 9-weekly for the first 26 weeks then 12-weekly thereafter), the definition of 2 missed visits will depend on the scheme.

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

If the 2 missed visits 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), two missing visits 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 subject has no evaluable disease assessments post-baseline or does not have baseline tumour assessment data they are censored at Day 1 unless they die within two visits of baseline (8 weeks plus 9 weeks plus 1 week allowing for a late assessment within the visit window) when the death date qualifies as a PFS event.

A summary of censoring rules and the date of PD/death or censoring are given in Table 4. Note that censoring overrides event in certain specified cases.

Table 4 Summary of Censoring Rules for PFS

Situation	Date of PD/Death or Censoring	PFS Outcome
Documented Progressive Disease (PD) or death in the absence of progression	Date of earliest documentation of PD or date of death in the absence of progression	Event
Either no tumour assessment at baseline or no evaluable assessments post-baseline	Date of death	Event

Table 4 Summary of Censoring Rules for PFS

Situation	Date of PD/Death or Censoring	PFS Outcome
AND death prior to second scheduled post-baseline disease assessment		
Either no tumour assessment at baseline or no evaluable assessments post-baseline AND no Death prior to second scheduled post-baseline disease assessment	Date of first dose (Day 1)	Censored
PD or death (in the absence of progression) immediately after ≥ 2 consecutive missed disease assessments as per the protocol specified assessment schedule	Last evaluable progression-free disease assessment prior to missed assessments	Censored
On-going with neither PD nor death at the time of analysis or lost to follow-up or withdrawn consent	Date of last evaluable disease assessment	Censored

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

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

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

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

The main analysis of PFS is based on the FAS. The number and percentage of subjects 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% confidence intervals will be estimated using the Kaplan-Meier method (if subject numbers allow).

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

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

Duration of follow-up for PFS is applicable only for PFS censored subjects and is defined as follows: Duration of follow-up for PFS (months) = (date of PFS event (progression/death) or censoring – date of first dose + 1) / (365.25/12).

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

4.10.3.5 Overall Survival (OS)

OS is defined as the time from date of first dose until the date of death from any cause, regardless of whether the subject withdraws from therapy or received another anti-cancer therapy.

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

Subjects who have not died by the analysis data cut-off date will be censored at their last date known to be alive before the cut-off date. Subjects known to be alive or dead after the data cut-off date will be censored at the data cut-off date. Subjects lost to follow-up will be censored at the date the subject is last known to have been alive.

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

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

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

- End of study date

The analysis of OS is based on the FAS. The number and percentage of subjects experiencing an OS event and Kaplan-Meier plots of OS will be presented. If subject numbers allow, the median OS and 2-sided 80% and 95% CI will be estimated using the Kaplan-Meier method.

Summaries of the number and percentage of subjects 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 will be presented separately for censored and non-censored subjects.

Duration of follow-up for OS is reported separately for censored subjects and non-censored subjects 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).

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

Supportive data: Change in Target Lesion Tumour Size

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

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 subject, taking the difference between each timepoint and baseline multiplied by 100 (ie, [timepoint – baseline]/baseline x 100).

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 visit at which the overall visit 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 subject has not died, progressed, or stated subsequent anti-cancer therapy.

Only response-evaluable subjects with measurable disease at baseline and at least one post baseline tumour assessment should be included in summaries of best percentage change in tumour size (measurable disease is as denoted on the CRF by the investigator).

The target lesion size and percentage change from baseline in target lesion size will be summarised using descriptive statistics and presented at each scheduled timepoint (refer to efficacy naming conventions in Section 4.2). Subjects 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 Week 8 assessment for these subjects.

Additionally, using scheduled and unscheduled tumour assessments 'spider' plots of percentage change from baseline in target lesion size by subject will be presented. A graphical summary of the best percentage change in the target lesion tumour size will be presented in a vertical bar chart with each subject's best percent change from baseline to nadir displayed as a vertical bar, with color coding that indicates best response attained ('waterfall' plot).

Supportive analysis:
As supportive analysis, the efficacy outcomes (ORR, CR and PR) may be presented by other relevant subgroups defined by AZ medical. This may include lymphoma classification, histology subtype, COO (GCB/non-GCB), prior CAR-T, BiTE and/or BTKi therapies.

4.10.4 Pharmacokinetics

4.10.4.1 Pharmacokinetic Concentrations

Plasma concentrations of AZD4573 plus acalabrutinib and its metabolite ACP-5862 will be listed by actual and relative (to dose administration) sampling time. Data from subjects excluded from the PK analysis set (ie, Safety Analysis Set) will be included in the data listings, but not in the descriptive statistics or in the inferential statistics. The following summary statistics will be presented for these concentrations and PK parameters at each time point by dose level:

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

- Number of observations

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

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

- If ≤50% of the concentrations are BLQ, all BLQ values will be set to the LLOQ, and all descriptive statistics will be calculated.
- If >50%, but not all, of the concentrations are BLQ, the geometric mean, geometric CV, arithmetic mean, and arithmetic 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 geometric CV, and arithmetic Std Dev, and 'BLQ' will be presented for geometric mean, arithmetic mean, median, minimum, and maximum.

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

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

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

The following figures, in black and white, will be generated for each of AZD4573, acalabrutinib and its metabolite ACP-5862:

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

Individual figures will be plotted using concentration versus actual time, and mean figures will be plotted using concentration versus nominal time, by treatment or dose level and cycle/PK day, as needed.

4.10.4.2 Pharmacokinetic Parameters Calculation and Summary

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

- Gmean (calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- gCV (calculated as 100 √ [exp(s2)-1], where s is the standard deviation of the data on a log scale)
- Gmean + gSD (gSD calculated as exp[μ±s])

- Gmean - gSD
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum
- Median
- Maximum
- Number of observations

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

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

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

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

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

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

4.11 Safety and Tolerability Evaluation

Module 1:

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

The Safety analysis set will be used for all safety and tolerability analyses. All listings and tables, other than those to assess DLTs will be based on the Safety Analysis Set. To describe the DLTs during Cycle 1 in Part A, the DLT-evaluable Analysis Set will be used. To describe DLT-like events beyond Cycle 1 all subjects who receive any amount of study treatment after Cycle 1 will be included.

Module 1 Parts A and B include AEs, AESIs, DLTs in Module 1 Part A Cycle 1, DLT-like events outside of the dose-setting evaluation period, laboratory data, vital signs, and ECGs as safety assessments. In Module 1 Part A, the safety assessments, which also include Cycle 1 DLTs for dose setting, are primary endpoints. In Module 1 Part B, the safety assessments are a secondary endpoint. Listings and summary tables and figures of all safety data for Module 1 Part A and Part B will be created as described in this section. In addition, for Module 1 Part A dose setting MTD (if determined) will be reported.

Module 2:

For Module 2 subjects, all safety data will be presented in separate listings and no summary tables will be provided.

The by subject listing will include the identification of the treatment period (Period 1/ Period 2) when the event occurred and/or the safety assessment was performed.

4.11.1 Exposure and treatment administration

Module 1:

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

Duration of AZD4573 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 subjects 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 of AZD4573 (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.

Duration of dose delays of AZD4573 will be derived for doses indicated as being delayed on the eCRF for subjects enrolled on CSP v3.0 and later versions. 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]. 9 is being used to account for the 2-day window. 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.

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.

- Duration of acalabrutinib exposure is defined by the last date of actual acalabrutinib dosing (ie, a dose > 0 mg was given) minus the date of first dose (> 0 mg) plus 1.
    - Duration of exposure acalabrutinib (weeks) = [min (last dose date where dose > 0 mg, date of death, date of DCO) – first dose date + 1]/7.
    - Actual duration of acalabrutinib exposure is the sum of duration of exposure – total duration of dosing delays.

Total and actual treatment duration will be summarised by descriptive statistics for each study drug (AZD4573 and acalabrutinib) and dose level/cohort, separately for Cycle 1 (including ramp-up) and for other treatment cycles. In addition, the number and percentage of subjects with at least one dose interruption will be summarised separately for Cycle 1 (including ramp-up) and for other treatment cycles, for each study drug. Exposure swimmer plot(s) will be produced, with a line presented for each subject to display relevant exposure and disposition details.

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

The following additional summaries will also be produced:

- Number of subjects that completed Cycle 1 (ending a week after receiving 12 mg AZD4573 for three times), including number of subjects that did not complete Cycle 1.
- Number of doses received per subject in Cycle 1.
- Total and actual duration of exposure, specific to Cycle 1.
- Number of subjects that initiated Cycle 2.

Module 1 Part A:

- Number of subjects that completed DLT evaluability period (all doses up to 3rd dose at target level), and number of subjects that did not complete DLT evaluability period
- Number of doses received per subject in DLT evaluability period (including subjects that did not complete DLT evaluability period)
- Actual treatment duration in weeks of exposure specific to DLT evaluability period (including subjects that did not complete DLT evaluability period)
- Number of subjects that initiated Post DLT Evaluability Period

Missed or forgotten doses

Missed and forgotten doses will be included in the listings for dosing but will not be included as dose interruptions in summary tables. However, missed doses will be included in the calculation of actual treatment duration.

Module 2:

For Module 2 subjects, actual and planned doses of AZD4573 and acalabrutinib will be appropriately listed by identifying the treatment period (Period 1/Period2) when the actual administration occurred.

4.11.2 Dose intensity

Module 1:

Dose intensity of AZD4573 and acalabrutinib will be addressed by considering relative dose intensity (RDI). RDI is the percentage of the actual dose delivered relative to the intended dose up to treatment discontinuation. RDI will be defined as:

The actual dose administered in mg of AZD4573 will be derived based on the actual volume (mL), planned dose (mg) collected in EDC, and the planned volume presented in Table 5 under “Total dose volume of diluted study drug (mL)”.

However, there was a high heterogeneity in the handling of AZD4573 preparations between the different sites (eg, some sites provided more diluted solutions which result in higher volume administered without an actual increase in dosing). To consider these different scenarios, the following rules for the derivation of actual dose (mg) will be applied:

- If actual volume (mL) < planned volume (mL):
  - actual dose (mg) = actual volume (mL)/planned volume (mL) x planned dose (mg)

- If actual volume (mL) > = planned volume (mL) and no overdose indicated in eCRF:
  - actual dose (mg) = planned dose (mg)
- If actual volume (mL) > = planned volume (mL) and overdose indicated in CRF:
  - actual dose (mg) = actual volume (mL)/planned volume (mL) x planned dose (mg)

Table 5: Examples of AZD4573 dose preparations

Dose (mg)	Required volume of study drug (mL)	Required volume of saline (mL)	Total dose volume of diluted study drug (mL)
1.5	1	60	61
3	2	100	102
6	4	250	254
9	6	250	256
12	8	250	258

Source: AZD4573 handling instructions

RDI (%) = 100 x 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.

The calculation of RDI for AZD4573 is illustrated with the following example. Assume a subject receives final dose of AZD4573 on Study Day 85. This subject was therefore 12.1 weeks (85/7) on treatment. The intended number of doses is therefore 13. From the above formula D = 6 + 9 + (12 x 11) = 147 mg. Assume the actual doses received by the subject is 6, 0, 6, 9, 12, 12, 12, 12, 0 and 12. From the above formula, d = 81 mg. RDI for the overall treatment period is therefore 100% x 81/147 = 55.1%. For the RDI in Cycle 1, d = 6 + 6 + 9 + 12 + 12 = 45 (Cycle 1 ends after receiving the 5th dose of AZD4573), and D = 6 + 9 + (12 x 3) = 51. The RDI in Cycle 1 is therefore 100% x 45/51 = 88.24%.

The following summaries will be produced:

- Summary of Interruptions (including duration of interruptions) and reductions of IP
- Summary of RDI
- Summary of intended and actual exposure AZD4573

Module 2:

The RDI will not be calculated and not presented for Module 2 subjects.

4.11.3 Dose limiting toxicities (DLTs)

Module 1:

DLTs contributing to dose setting in Module 1 Part A Cycle 1 will be listed and summarised separately from AEs which meet the DLT definition criteria but are presented after the initial DLT setting assessment period in Module 1 Part A or in Module 1 Part B (DLT like-events).

The DLT criteria are defined in Section 15.3 of the CSP.

The number of Module 1 Part A dose-setting subjects evaluable for determination of DLTs during the DLT-assessment period and the number of subjects with any DLT will be summarised by dose level. For analysis reporting purposes, the DLTs are as approved and documented at the Safety Review Committee meetings. Excel spreadsheet created manually from the SRC meeting minutes and checked independently by another individual will be shared with the "DLT Evaluability =Y/N" information. The MTD will be selected from all tried dose levels that have not been previously declared to be unsafe with a DU decision according to the mTPI-2 algorithm (see CSP Section 15.2). With this constraint, the MTD will be determined as the dose level with the DLT estimate closest to the target toxicity level of 30%. The MTD will be determined by isotonic regression analysis applied to DLT rates observed in the DLT-assessment period during dose exploration using the mTPI-2 method In the case of dose levels with estimated toxicity of equal distance (tied dose levels) from the target toxicity of 30%, the following approach is used: among all tied dose levels the highest dose level with target toxicity ≤ 30% will be selected, unless all tied dose levels have estimated toxicity > 30%, in which case the lowest dose level will be selected.

For Module 1 Part B subjects in meeting the same criteria for DLT evaluability that were used for Module 1 Part A dose setting, the number and percentage with any DLT-like event reported as an adverse event, will be summarised.

For pooled RP2D-treated Module 1 Part A and Part B subjects that received 3 AZD4573 doses at target level, the number and percentage that experienced at least one DLT-like event reported as an adverse event after receiving any further amount of study treatment will be summarised.

Types of DLTs and DLT-like events and numbers of events per subject will also be summarised.

Module 2:

This section is not applicable to Module 2 subjects.

4.11.4 Adverse Events

Adverse Events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1 or higher and will be graded according to the National Cancer Institute of Common Terminology Criteria for AEs (CTCAE version 5.0).

AEs are defined as treatment emergent (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-treatment severity of the AE recorded closest to the start of dosing.

When assigning AEs to the relevant phase of the study the following rules will apply:

- Pre-treatment phase – All AEs with a start date after signing the informed consent form (ICF), prior to the first administration of IP that do not subsequently go on to worsen during the treatment emergent phase.
- Treatment emergent phase – All AEs starting or worsening (severity) following the first administration of IP for the duration of the treatment period, up to and including 30 days after the last dose of study treatment as per the study safety follow-up period but prior to subsequent cancer therapy. AEs with a missing start time which occur on the same day as first IP administration are reported as treatment emergent. Note that the treatment emergent phase includes the on treatment and safety follow-up periods.
- Off-treatment phase – All AEs starting more than 30 days after last dose of study treatment or once subsequent cancer therapy is started, whichever is earlier.

Serious AEs (SAEs)

A SAE is any AE that:

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

AEs of Special Interest (AESIs)

The following are considered to be AESIs for AZD4573:

- Tumour lysis syndrome (TLS) (see Section 4.11.12)
- Hepatotoxicity (including Potential Hy's Law (PHL), Drug-induced liver injury (DILI), and Bilirubin increase with transaminase increase (ALT or AST or both).
- Neutropenia (including Febrile neutropenia, Neutropenic sepsis, and Neutrophil count decrease)
- Thrombocytopenia, including Platelet count decrease
- Myocardial ischaemia
- Pyrexia

The following are AESIs for acalabrutinib:

- Ventricular arrhythmias (eg, ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation).

Other significant adverse events (OAE)

The list of AESI is comprehensive and no OAEs are not defined.

4.11.5 Deaths

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

- Related to disease under investigation only
- AE outcome=death only
- AE with outcome of death only (AE start date falling after 30 day follow up period)
- Both related to disease under investigation and with AE outcome = death
- Other deaths

A corresponding listing will also be produced.

4.11.6 Clinical Laboratory, Blood Sample

4.11.6.1 Definitions and Derivations

All local laboratory results collected will be listed (refer to Section 17.1.6, 17.1.7 and Section 10.2 of the CSP for the list of clinical safety laboratory tests to be performed and the SoA for timing and frequency).

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 6.

Table 6: Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**	
B-Blasts	S-Albumin	S-C Reactive Protein
B-Blasts/Leukocytes	S-Alkaline Phosphatase (ALP)	S-Factor V Leiden
B-Hematocrit	S-Alanine Aminotransferase (ALT)	S-Gamma Glutamyl Transferase (GGT)
B-Hemoglobin	S-Aspartate Aminotransferase (AST)	S-Glucose
B-Leukocytes (white blood cell count)	S-Bicarbonate	S-Lactate Dehydrogenase (LDH)
B-Lymphocytes (ALC)	S-Direct Bilirubin	S-Magnesium
B-Lymphocytes/Leukocytes	S-Bilirubin (BILI)	S-Phosphate

B-Platelet	S-Indirect Bilirubin	S-Potassium
	S-Calcium	S-Protein
Coagulation	S-Cholesterol	S-Sodium
Activated partial thromboplastin time (APTT)/Prothrombin time (PT)	S-Creatine Kinase (CK or CPK)	S-Triglycerides
Prothrombin international normalized ratio (INR)	S-Chloride	S-Urate
D-dimer (where available at institution)	S-Creatinine	S-Urea Nitrogen
Fibrinogen	S-Creatinine Clearance	
Urinalysis (dipstick)		
U- Erythrocytes/Blood	U-Glucose	U-Protein
U-Ketones		

Abbreviations: B=blood; P=plasma; S=serum; U=urinalysis.

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

Liver Function Parameters

Subjects with elevated post-baseline ALT, AST, or Total Bilirubin will be identified. The number and percentages of these subjects will be tabulated.

4.11.6.2 Presentations

All clinical laboratory results will be listed.

For all continuous laboratory assessments, absolute values, change from baseline will be summarised using descriptive statistics at each time point by dose level/cohort. Box plots of absolute values and change from baseline values for haematology and clinical chemistry parameters will also be presented.

For clinical haematology, clinical chemistry and coagulation endpoints, shift tables from baseline to worst on-treatment value according to reference range classification will be created. CTCAE grade changes from baseline to the maximum on-treatment grade will also be provided. In addition, the number of subjects with $\geqslant$ 2 CTCAE grade changes and CTCAE grade changes of 3 or 4 will be summarised by actual dose level/cohort for clinical chemistry and haematology parameters.

Liver Function Parameters

For subjects with "Potential Hy's law", the change in the following laboratory parameters from baseline to each post-baseline visit will be summarized: ALT, AST, ALP, GLDH, LDH, GGT, and INR. Individual subject data for these laboratory parameters will be listed as well.

Plots for both maximum post-baseline ALT and AST versus the maximum post-baseline BILI (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 subjects with elevated ALT or AST (≥ 3 x ULN) and elevated bilirubin (≥ 2 x ULN,) regardless of whether or not these elevations occurred at the same visit, or ALT or AST of ≥ 5 x ULN, will be tabulated and plotted.

4.11.7 Clinical Laboratory, Urinalysis

4.11.7.1 Definitions and Derivations

Urinalysis variables that will be measured are detailed in Table 6.

4.11.7.2 Presentations

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

4.11.8 Vital Signs

The following vital signs will be assessed and listed:

- Systolic blood pressure (SBP) [mmHg]
- Diastolic blood pressure (DBP) [mmHg]
- Pulse rate (bpm)
- Oral body temperature (°C)
- Weight (Kg)
- Height (cm)

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

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

Absolute values and change from baseline blood pressure and pulse rate will be presented in box plots.

4.11.9 ECGs

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

- RR-interval (msec)
- QRS-interval (msec)
- RR-interval (msec)
- QT-interval (msec)

- QTc-interval (msec)
- QT-interval corrected using the Fridericia correction formula (QTcF) (msec)
- Heart rate (beats per minute [bpm])

From these resting 12-lead ECGs values of the QT and RR intervals, the QTcF will be rederived using the following formula:

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

The ECG will be evaluated by the Investigator as 'Normal', 'Abnormal' or 'Borderline'.

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

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

The average of the three individual tracings will be used in summaries and listings. The individual tracings will be also displayed in the data listings.

Box plots of absolute values and change from baseline in ECG parameters over time will be presented.

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

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

The result of echocardiograms at screening and after an abnormal ECG finding (T wave inversion/flattening) will be listed and, if appropriate, presented in a summary table. In addition, the results of all multi-gated acquisition (MUGA) scans to assess left ventricular ejection fraction (LVEF) will be listed. ECG data will be collected by ERT.

4.11.10 Physical Examination

The physical examination will include general appearance of the subject, examination of the skin, eyes, ears, nose, throat, respiratory system, cardiovascular system, abdominal cavity. extremities, musculoskeletal system, lymphatic system, and neurological. Physical Examination results will be listed by subject.

4.11.11 Eastern Cooperative Oncology Group performance status (ECOG PS)

ECOG performance status scores will be assessed at screening and before each dose of AZD4573 according to ECOG criteria as follows:

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

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

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

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

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

5= Death

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

4.11.12 B Symptoms

Information on B symptoms (Unintentional Weight Loss within 6 Months, 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 visit, comments) will be listed for all subjects and visits.

4.11.13 Tumour lysis syndrome

Tumour lysis syndrome (TLS) is an important identified risk for AZD4573 and an identified risk for acalabrutinib. Subjects will be required to be monitored for TLS for up to 24 hours post dose until they have received at least one AZD4573 dose at the target dose level (ie, for at least the first 3 AZD4573 once-weekly doses), and data will be recorded on the TLS Monitoring forms.
During these TLS assessment periods, blood samples will be collected pre-dose and every 4-6 hours until 24 hours after infusion, for analysis of potassium, calcium, phosphate, uric acid, creatinine and blood urea nitrogen, and subjects will be monitored for clinical signs of TLS (increased creatinine, cardiac arrhythmia, seizure). Laboratory values and clinical signs of TLS occurring during the TLS assessment periods are recorded and evaluated according to Cairo-Bishop criteria under CSP version 1 2, 3 and according to Howard Modification of Cairo-Bishop under CSP version 3, 4, and 5.

If laboratory findings met the Cairo-Bishop criteria for laboratory TLS investigators are instructed to record an AE of laboratory/biochemical TLS. If a clinical sign of TLS is present for the same assessment period as laboratory findings consistent with laboratory TLS, Investigators are instructed to only record an AE of clinical TLS. Thus, there are two data sources contributing to the analysis of TLS: TLS monitoring data and AE data.

All laboratory TLS data will be summarized and presented by dose level under one overall category named “Laboratory TLS confirmed by Cairo-Bishop criteria or Howard Modification of Cairo-Bishop criteria”.

The different TLS laboratory subcategories will be presented under those defined Cairo-Bishop criteria as are considered the most inclusive categories. For example, “Laboratory TLS criteria met: Potassium (>= 6.0 mmol/L or 6 mg/L)” will be counted under the category “Potassium (>= 6.0 mmol/L or 6 mg/L) or 25% increase from baseline”.

TLS monitoring data

According to the TLS monitoring schedule in CSP Section 10.2 for Module 1 and Section 19.2 for Module 2 which includes multiple scheduled assessment time points after each infusion of study drug, subjects could have multiple records of “TLS confirmed? = Yes” per infusion. “TLS confirmed? = Yes” means that at least laboratory TLS criteria have been met. TLS monitoring data will be summarised per infusion at episode-level (subjects may have a TLS episode after more than one infusion) and subject-level. A maximum of one TLS episode per infusion per subject will be counted for each infusion. For records of “TLS confirmed? = Yes” and clinical TLS (subjects with data supporting a clinical grading entry for one or more of creatinine abnormality, cardiac arrhythmia, seizure):

- The highest Investigator-assigned clinical Cairo-Bishop grade per infusion and per subject will be summarised separately for creatinine abnormality, cardiac arrhythmia, and seizure.
- The overall Cairo-Bishop grade will be derived based on the highest contributing Investigator-assigned clinical grade (among grades for creatinine abnormality, cardiac arrhythmia, seizure) for each record of clinical TLS; the highest derived overall Cairo-Bishop grade per infusion and per subject will be summarised.
- The number of infusion episodes of TLS per subject will be described categorically and using summary statistics. Time to first onset of TLS (hours from start of infusion to first onset of TLS) will be described using summary statistics according to the earliest timepoint with “TLS confirmed? = Yes” (including subjects without clinical TLS).

Time to first onset of TLS (hours from start of infusion to first onset of TLS) will be described using summary statistics according to the earliest timepoint with “TLS confirmed? = Yes” (including subjects without clinical TLS).

AE data

Investigators can report AEs at any time during the study period, hence reporting of AEs of TLS is not restricted to the 24-hour period after each infusion of study treatment during the ramp-up period. Accordingly, there may be a discrepancy between the number of subjects with an AE of TLS and the number of subjects with a TLS monitoring record of “TLS confirmed? = Yes". As each CTCAE grade change will be recorded as a separate AE in this study, subjects may have more than one AE record during continuous occurrence of TLS if the severity of TLS changed before resolution. Subject-level summaries will present the maximum CTCAE grade for each subject, event level summaries will present the maximum CTCAE grade for each continuous occurrence. In addition to presentation by MedDRA PT and CTCAE grade within standard AE tables and listings, AEs of TLS will also be presented by MedDRA LLT, as this level of the hierarchy allows distinction between clinical and

laboratory TLS. The number and percentage of subjects with an AE of LLT clinical TLS, laboratory TLS or (unspecified) TLS will be presented by maximum CTCAE grade, and total numbers of AEs. Bar charts showing the number of AEs of TLS and the number and percentage of subjects with AEs of TLS by week since first AZD4573 administration will be presented. Time to first onset of any AE of TLS (days) since first AZD4573 administration will be described using summary statistics.

4.11.14 Other Safety Assessments

4.11.14.1 Presentations

Serum immunoglobulins (IgA, IgM, IgG) will be listed and summarized descriptively.

4.12 Interim Analyses

No interim analyses are planned for the study due to the decision to permanently halt enrolment.

4.13 Determination of Sample Size

Refer to Section 18.2 of the CSP for Module 1 and Section 27.2 of the CSP for Module 2.

4.14 Changes or Clarification to Protocol in the Conduct of the Study or Planned Analysis

CSP version 5.0 is describing the entire statistical analysis originally planned for Module 2, however due to the limited sample size (ie, 3 subjects treated), Module 2 data will not be presented in summary tables and only by-subject listings and figures will be produced.

5 REFERENCES

Cairo and Bishop 2004
Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127(1):3-11.

Cheson et al 2014
Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluations, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano Classification. J Clin Oncol 2014;32:3059-68.

Guo et al 2017
Guo W, Wang SJ, Yang S, Lynn H, Ji Y. A Bayesian interval dose-finding design addressing Ockham's razor: mTPI-2. Contemp Clin Trials. 2017;58:23-33

6 APPENDICES

Module 1 - Part A subjects to be included in Part B analysis
PURPOSE:
This document describes the process for using data from subjects enrolled in Module 1 Part A in analyses for Module 1 Part B. This document describes:

- the process for Cell of Origin (COO) testing, used to identify GCB and non-GCB DLBCL subjects;
- the selection criteria for Part A subjects whose data will be included in the final analysis for Part B;
- the process to document the recycling of Part A subjects data.

PROCESS
1. Cell of Origin (for all part A and part B subjects)
For the purposes of recycling of data from Part A subjects for analysis with Part B subjects data, COO data from local assessment will be used.
2. Definition of Part A subjects that will be included in the Module 1 Part B final analysis
Data from Module 1 Part A subjects will be analysed together with data from Part B subjects if the Part A subjects fulfil all the conditions below:

- Must have received any amount of AZD4573 and acalabrutinib on study;
- Must have been enrolled in the 12 mg (RP2D) dose level cohort;
- Must have a diagnosis of de novo DLBCL, ie:
    - DLBCL NOS (de novo), or
    - High-Grade B cell Lymphoma (NOS), or
    - High-Grade B cell Lymphoma with MYC and BCL2 and/or BCL6 rearrangements;
- Must have measurable disease at baseline (ie be part of the response evaluable set).

3. Documentation of review and confirmation
The Parexel Programming team will programmatically identify Part A subjects whose data can be recycled in Part B for final analysis purposes, based on the criteria described in this document. Subjects that can be recycled will be marked by population flags in the ADAM and SDTM specifications. TFLs will be generated including the correct individuals (including recycled subjects) in each cohort; a listing of recycled subjects will also be included in the TFLs.

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