Clinical Study Protocol	
Study Intervention	AZD4573
Study Code	D8230C00002
Version	5.0
Date	01 June 2023

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

Sponsor Name: AstraZeneca AB

Legal Registered Address: AstraZeneca AB, 151 85 Södertälje, Sweden.

Regulatory Agency Identifier Number(s)

European Clinical Trials Database (EudraCT) number: 2020-001642-18

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4, Version 5	01 June 2023
Amendment 3, Version 4	01 August 2022
Amendment 2, Version 3	21 July 2021
Amendment 1, Version 2	03 July 2020
Version 1	30 April 2020

Amendment 4, 01 June 2023

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

Overall rationale for the Amendment

Since Study D8230C00002 was first opened (in July 2020) significant challenges have occurred with recruitment into both Module 1 and Module 2. These challenges precluded completion enrolment within the allocated timeframe of January 2023. AstraZeneca has therefore taken the decision to stop recruitment into the study. The decision was not prompted by any new or altered safety concern with AZD4573 or acalabrutinib and has no impact on the overall risk-benefit assessment for either IMP. Based on this decision, the main purpose of this protocol amendment is to add a rationale for the proposed reduction in scope of study D8230C00002 and to set out measures to allow participants still receiving clinical benefit of the study treatment after data collection for the primary analysis has completed to continue study treatment. End of study definitions and scope of data collection are updated to describe this scenario

End of study definitions and scope of data collection are updated to describe this scenario.

See table below for a summary of the main changes. Additionally, typographical errors were corrected, and minor edits made in the protocol text where needed.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
4.1: Overall Design	Rationale added as to why recruitment into the study has permanently halted.	During the study, significant challenges have occurred with recruitment into	Substantial

	Text added to define that participants still receiving clinical benefit of the study treatment after data collection for the primary analysis may continue to receive the study treatment. Text added as to the initially planned interim analysis will not be performed and that the results from the Module 1 DLBCL cohorts will be pooled for the purpose of the primary analysis. The following text was added: "Since Study D8230C00002 was first opened (in July 2020) significant challenges have occurred with recruitment into both Module 1 and Module 2. These challenges precluded completion enrolment within the allocated timeframe of January 2023. AstraZeneca has therefore taken the decision to stop recruitment into the study. Based on this decision, the main purpose of this protocol amendment is to add a rationale for the	both Module 1 and Module 2, which are likely to preclude completion of the study within the previously allocated timeframe.	

	proposed reduction in scope of study D8230C00002 and to set out measures to allow participants s still receiving clinical benefit of the study treatment after data collection for the primary analysis has completed to continue study treatment. End of study definitions and scope of data collection are updated to describe this scenario"		
8.2.10: Reporting of Serious Adverse Events	Text added: "Participants continuing study treatment after the end of data collection for the primary analysis will be followed for SAEs with paper reporting instead of eCRF reporting."	Clarification that no eCRF reporting will be applicable following the end of data collection	Non-substantial
13.1: Overall Design	Clarification added on possible dose escalation decisions for Module 1, based on existing statistical model. (± Equivalence Interval Margin) added.	Clarification of how the mTPI-2 method will be implemented	Non-Substantial
4.5: End of Study Definition 13.4: End of Study Definition	The end of study definition in the Core section of the protocol was updated. The language was updated to state that the	Defining end of study and allowing Module 1 participants to continue receiving treatment after the data cut-off date, if	Substantial

	last visit of the study will be the date when the last participant permanently discontinued treatment with all investigational products. The end of study definition for participants enrolled was updated. Text was added to describe treatment continuation, data collection and clinical database closure due to the early permanently halted enrolment.	still receiving clinical benefit.	
15.6: Definition of DLT-evaluable Participant, Table 21	Module 1 definition of "DLT-evaluable participant" clarified	Clarification per memo "Information regarding protocol inconsistencies" 10 March 2022	Non-Substantial
6.13: Intervention after the end of the study 15.13: Intervention after the end of the study 15.7: Duration of therapy	Text was added, allowing Module 1 participants to continue receiving study intervention after the end of the study if, in the opinion of the Investigator, they are still receiving clinical benefit from treatment. CCI [redacted]	For ethical reasons, participants should have the possibility to continue treatment if applicable The Investigator should continue to monitor the participant for SAEs following the end of data collection CCI [redacted]	Substantial

	CCI [redacted]		
17.1.9.3: Survival Follow-up	"...third party" was removed. "In preparation for an analysis, survival calls will be made in the week following the data-cut-off for the analysis" was added. The text was updated to clarify that the follow-up calls/clinic visits for survival should occur starting 3 months after end of treatment/discontinuation	No third-party will be used Survival calls will identify if any Module 1 participants should be censored following data-cut-off Clarification as to when the follow-up calls will start	Non-substantial
18.3: Populations for analyses, Table 22	"Modified response evaluable" changed to "Interim response evaluable"	Clarification	Non-Substantial
18.4.5.1: Objective Response Rate and Proportion of Participants with Complete Response	Clarifying text was added to define OR, ORR, and CRR	Clarification	Non-Substantial
18.4.5.2: Time to response	Re-worded to clarify definition of TTR	Clarification	Non-Substantial
18.4.5.3: Duration of response	Clarification of DoR	Clarification	Non-substantial

27.4.5.3: Duration of response			
18.5 Interim analyses	Section text deleted and "No interim analyses are planned for the study due to the decision to permanently halt enrolment" added.	No interim analyses planned for Module 1, due to early primary analysis following permanently halted enrolment	Substantial
26.1.7: Clinical Safety Laboratory Assessments	Clarification that the TLS monitoring applies to Period 1 and 2	Clarification	Non-substantial
26.1.9.3: Survival Follow-up	"...third party" was removed	No third-party will be used	Non-substantial
18.3: Population for Analyses, Table 22 27.3: Populations for Analyses, Table 43	"modified response evaluable" changed to "interim response evaluable"	Clarification	Non-Substantial
Throughout document	The word "patient" is exchanged to "participant"	Align with standard wording recommended by health authorities	Non-substantial

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: 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

Short Title: AZD4573 in Novel Combinations with Anti-cancer Agents in Patients with Advanced Haematological Malignancies

Rationale: AZD4573 (formerly known as AZ13810325) is a potent and selective inhibitor of cyclin-dependent kinase 9 (CDK9) with nanomolar potency against the enzyme (half maximal inhibitory concentration [IC50 < 4 nM]) and excellent selectivity over other CDK family members. AZD4573 decreases pSer2RNAP2 levels [the phosphorylation levels of Ser2 found in the carboxyl-terminus domain (CTD) of RNA polymerase II (RNAP2)]. This decrease in pSer2RNAP2 is linked to preferential reduction of labile proteins like the B-cell lymphoma 2 (BCL2) family anti-apoptotics Mcl-1 and Bfl-1 as well as other well-known oncoproteins like myelocytomatosis (MYC), which leads to rapid induction of apoptosis in a broad range of human cancer cell lines derived from haematological malignancies. AZD4573 demonstrates significant anti-tumour activity in vivo associated with transient CDK9 inhibition across a range of tumour xenograft models as a single agent when dosed intermittently.

AZD4573 may therefore have the potential to provide clinical benefit in terms of anti-tumour activity in participants with selected haematological malignancies who have relapsed after, or are refractory to prior standard therapy, and for whom there is no other standard therapy available. AZD4573 is a novel targeted agent that has shown activity across a range of haematological malignancy models and has also demonstrated improved depth and duration of response (DoR) when combined with a number of standard-of-care (SoC) or other targeted agents in vivo.

The mechanism of action and in vivo data in nonclinical models suggest the potential to combine AZD4573 with a number of other anti-cancer treatments, resulting in either synergistic or additive activity. This study is modular in design, allowing evaluation of the safety, efficacy, and tolerability of AZD4573 in novel combinations with other anti-cancer agents. Further modules will be added via protocol amendment. Study information applicable to all participants in this study will be described in the core section of this protocol; the rationale for each combination and treatment arm, and specific study information and assessments will be described in each separate module.

There are two parts to each combination module of this study:

- Part A: Phase I dose setting (dose confirmation in Module 2) to assess safety and tolerability and determine/confirm dose(s) and schedule(s) of each combination treatment to be evaluated in Part B.
- Part B: Phase II cohort expansions in select participant groups to assess preliminary anti-tumour efficacy of each combination treatment.

Initiation of Part B for each module will depend on the evaluation of safety outcomes in Part A. The addition of new modules will depend on evaluation of preclinical data showing a synergistic or additive effect of AD4573 in combination with other anti-cancer agents in the relevant disease model.

This protocol refers to the following modules and study drugs:

AZD4573 Combination Therapy with Acalabrutinib - Modules 1 and 2

Acalabrutinib is a selective, irreversible small molecule Bruton's tyrosine kinase (BTK) inhibitor. In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Acalabrutinib and its major metabolite ACP-5862 inactivate BTK by forming a covalent bond with a cysteine residue in the kinase active site. This leads to inhibition of signaling through the B-cell receptor (BCR) in sensitive cells. In nonclinical and clinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and survival.

Acalabrutinib is also known as ACP-196 and Calquence®. Calquence is approved in the United States and is either approved or under regulatory assessment in other countries as:

- Monotherapy for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.
- Monotherapy and in combination with obinutuzumab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).

Module 1: AZD4573 + acalabrutinib in participants with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) or relapsed or refractory marginal zone lymphoma (MZL).

Data with AZD4573 in combination with acalabrutinib in an activated B-cell (ABC) DLBCL xenograft model have shown an increase in both the magnitude and duration of anti-tumour

response compared with either single agent alone. In addition, given acalabrutinib's previously demonstrated activity in B-cell malignancies, its initial demonstration of activity in the difficult-to-treat population of relapsed/refractory (r/r) DLBCL as monotherapy, and mechanism of action (non-overlapping with CDK9 inhibitors), combination therapy with acalabrutinib and AZD4573 may reasonably be expected to yield greater clinical benefit than with either agent alone.

The first generation BTK inhibitor ibrutinib is Food and Drug Administration (FDA)-approved for treatment of patients with MZL requiring systemic therapy who have received at least one prior anti-CD20-based therapy. However, there remains an unmet need for treatment of patients with advanced MZL.

AZD4573 decreases pSer2RNAP2 levels linked to reduction of Mcl-1, Bfl-1 and Myc proteins and is associated with rapid and preferential induction of apoptosis in a broad range of human cancer cell lines derived from patients with haematological malignancies. Mcl-1 expression has been evaluated in human B-cell lymphomas, including MZL (Cho-Vega et al 2004). Mcl-1 was expressed across different subtypes of MZL: in 4 of 5 (80%) nodal and splenic marginal zone B-cell lymphoma, and 4 of 11 (36%) extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type. Given the demonstrated activity of BTK inhibitors in MZL (Lue et al 2020), their relatively well-tolerated safety profile, and a mechanism of action that is non-overlapping with CDK9 inhibitors, it is hypothesised that combination therapy with AZD4573 and acalabrutinib may yield greater clinical benefit than with either agent alone in patients with MZL.

Part A of Module 1 will enrol participants with r/r diffuse DLBCL or r/r MZL who have failed prior therapy(ies), are not eligible for curative treatment options, and for whom there is no standard therapy available.

In Part B, separate expansion cohorts for DLBCL germinal centre B-cell (GCB) and non-GCB subtypes will be opened at the recommended Phase II dose (RP2D). A further expansion in MZL participants may be opened by a protocol amendment, based on emerging clinical data.

Module 2: AZD4573 monotherapy window followed by AZD4573 + acalabrutinib in participants with relapsed or refractory MCL.

Acalabrutinib, a potent and selective BTK inhibitor, is approved by the FDA for the treatment of adults with MCL who have received at least one prior therapy. In a Phase II study of acalabrutinib involving 124 participants with relapsed or refractory (r/r) MCL, 81% of participants had a complete response (CR 40%) or partial response (PR 41%) after a median of 15.2 months of follow-up. Kaplan-Meier (KM) estimates of median Duration of Response (DoR), progression-free survival (PFS) and overall- survival (OS) were not reached

(Wang et al 2018). At long-term follow-up after a median of 38.1 months, the median DoR was 28.6 months (95% confidence interval (CI) 17.5-39.1 months] and median PFS was 22.0 months (16.6-33.3 months) (Wang et al 2020).

Part A of Module 2 is a window study comprising 2 cycles (8 weeks) of AZD4573 monotherapy (Period 1) followed by AZD4573 + acalabrutinib combination treatment (Period 2). It will enrol participants with r/r MCL who have failed at least one line of prior therapy, are not eligible for curative treatment options. AZD4573 will be administered as monotherapy (at the R2PD from the ongoing FTIH study [D8230C00001] in DLBCL) and in combination with acalabrutinib 100 mg twice daily. The dose of AZD4573 in combination with acalabrutinib will be the RP2D determined in Module 1 Part A.

The study design of Part B of Module 2 will be determined from the data emerging from Part A. Specifics of Part B will be defined in a future protocol amendment.

Additional modules and combinations of AZD4573 with other anti-cancer agents may be added in the future by amendment.

Objectives and Endpoints Applicable to all Modules

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
Part A	
• Assess the safety and tolerability, describe the DLTs, and identify the MTD and/or RP2D of AZD4573 when administered intravenously to participants with advanced relapsed/refractory haematological malignancies, in novel combinations with other anti-cancer agents[a]	• Adverse events, DLTs, laboratory data, vital signs, and ECG changes
Part B	
• Assess the efficacy of AZD4573 in novel combinations with other anti-cancer agents in participants with relapsed/refractory haematological malignancies	• Refer to Modules for endpoints
Secondary	
Part A and B	
• Assess the plasma/serum PK of AZD4573 and other anti-cancer agents when given in combination	• Plasma concentrations and derived PK parameters for AZD4573 summarised

Objectives	Endpoints
	by cohort and dose level for the PK analysis set • Plasma/serum concentrations and derived PK parameters for other anti-cancer agents summarised by cohort and dose level for the PK analysis set
Part B	
• Further assess efficacy of AZD4573 in novel combinations with other anti-cancer agents	• Refer to Modules for endpoints
• Assess the safety and tolerability of the RP2D of AZD4573 in novel combinations with other anti-cancer agents	• Adverse events, laboratory data, vital signs, and ECG changes

[a] If the MTD and RP2D have already been set in another disease population, the dose setting phase can be a dose-confirmation phase.

Abbreviations: DLT = dose-limiting toxicity; ECG = electrocardiogram; MTD = maximum tolerated dose; PK = pharmacokinetics; RP2D = recommended Phase II dose.

CCI Refer to the individual study modules of the protocol for detailed objectives and endpoints.

Overall Design

This is a modular, multicentre, open-label, non-randomised, Phase I/II, dose-setting and expansion study including an intra-patient ramp up, designed to investigate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary activity of AZD4573 in novel combinations with other anti-cancer agents in participants with select r/r haematological malignancies.

This is a non-randomised study. Each potential participant approved for screening is assigned a unique participant enrolment number. If a participant withdraws from the study, then the enrolment number cannot be reused.

A study-specific Safety Review Committee (SRC), in accordance with its charter, will be responsible for providing ongoing safety surveillance of the study, with regularly scheduled reviews of safety, PK, and other relevant data.

Part A of each module will identify the maximum tolerated dose (MTD) and/or RP2D of AZD4573 in combination with other anti-cancer agents. If the MTD and RP2D have been set

in a given disease population, the dose setting phase can be a dose confirmation phase. In Module 1, the initial target dose of AZD4573 selected for this study in combination with other anti-cancer agents will be attained by an intra-patient ramp up during the first cycle of treatment. A recommendation about the dose level for each next cohort of evaluable participants will be made by the SRC, guided by decision rules provided in study modules. For example, in Module 1 the decision rules are based on a modified toxicity probability interval (mTPI-2) design with a 30% target dose-limiting toxicity (DLT) rate (± 5%) for MTD: dose escalation, stay at the current dose, de-escalation, or de-escalation and current dose is unsafe so will never be used again due to unacceptable toxicity.

In Part B (expansion) of each module, separate expansion cohorts for participant subgroups will be opened in order to further assess safety and tolerability, and explore anti-tumour activity of particular drug combinations.

Module 1

Module 1, Part A will enrol 'all-comer' participants with r/r large B-cell lymphoma including subtypes such as DLBCL not otherwise specified [NOS], high-grade B-cell lymphoma [HGBCL], primary mediastinal large B-cell lymphoma [PMBCL], or large B-cell lymphoma transformed from indolent B-cell lymphomas (including but not limited to Richter Syndrome, transformed Follicular Lymphoma, transformed MZL), or r/r MZL, who have failed prior therapy(ies), are not eligible for curative treatment options, and for whom there is no standard therapy available. A 5-week DLT-assessment period will incorporate the whole of Cycle 1, including the dose ramp up and the first 3 weeks at the target dose.

Dosing will be staggered by at least one week between the first and the second participant dosed in each new dose level cohort. Subsequent participants dosed will be staggered by a minimum of 3 days until a decision is made regarding dose escalation or de-escalation.

Module 1, Part B will enrol only participants with r/r de novo DLBCL and will focus on evaluating the preliminary efficacy of combination therapy in GCB and non-GCB subtypes in two separate expansion cohorts.

Module 1 will enrol participants at approximately 30 sites in approximately 10 countries.

Module 2

Module 2, Part A will enrol participants with r/r MCL who have failed at least one line of prior therapy.

Part A will have 2 dosing periods. Period 1 will explore once-weekly intravenous (IV) administration of AZD4573 12 mg monotherapy. Period 1 will confirm in MCL the AZD4573 monotherapy RP2D dose that was established in DLBCL in the first-time-in-human (FTIH)

study (D8230C00001), as the dose setting in the FTIH study did not include participants with MCL. In Period 1, participants will receive AZD4573 6 mg at Cycle 1 Week 1 and AZD4573 9 mg at Cycle1 Week 2, then AZD4573 12 mg weekly thereafter. Period 2 will assess the safety and tolerability of AZD4573 administered in combination with oral acalabrutinib.

Specifics of Part B study design will be defined in a future protocol amendment.

Disclosure Statement: This is a non-randomised, open-label, sequential, dose setting and expansion treatment study with no masking.

Number of Participants:

In **Module 1**, depending on dose escalation/de-escalation and enrolment in the expansion groups, up to a maximum of 105 participants will be treated with AZD4573 + acalabrutinib.

In Module 1 Part A (dose setting), 3 to 9 evaluable participants may be treated in each of up to 3 dose levels using an mTPI-2 design permitting up to a maximum of 24 DLT-evaluable participants for dose setting (ie, a maximum of 9 evaluable participants at each of two dose levels and 6 evaluable participants at the third dose level). In addition, any safe dose level may be backfilled to include up to approximately 21 evaluable participants to collect additional tolerability, PK[redacted] The maximum number of evaluable participants in Part A is therefore 63. In Part B (expansion), separate RP2D expansion cohorts will be opened for GCB and non-GCB DLBCL subtypes. For primary analyses, a total of approximately 21 RP2D-treated response-evaluable participants of GCB subtype and approximately 21 RP2D-treated response-evaluable participants of non-GCB subtype will be incorporated, including participants from Part A and Part B. The total number of evaluable participants treated in Part B will be up to approximately 42.

In **Module 2,** approximately12 participants in Part A will receive monotherapy with AZD4573 (with intra-patient ramp up), followed by administration of AZD4573 in combination with acalabrutinib. The study design of Part B of this module, including number of participants, will be determined from the data emerging from Part A.

Intervention Groups and Duration:

Duration of therapy will be defined in specific modules.

In **Module 1** (AZD4573 + acalabrutinib combination therapy), treatment with AZD4573 and acalabrutinib, in Part A and Part B, may be continued until disease progression, an unacceptable drug-related toxicity occurs, or the participant withdraws or is withdrawn from the study as defined in the protocol.

In Part A (dose setting), this study module will initially explore once-weekly intravenous (IV) administration of AZD4573 at up to 3 target dose levels in combination with oral acalabrutinib 100 mg twice daily and will enrol all-comer participants with DLBCL or MZL.

In Part B (expansion), separate expansion cohorts for GCB and non-GCB DLBCL subtypes will be opened at the RP2D.

For both Part A and Part B of Module 1, Cycle 1 consists of 5 weeks (DLT-assessment period in Part A), including an intra-patient dose ramp up. Subsequent cycles are 21 days (3 weeks) with once-weekly dosing of AZD4573 in combination with acalabrutinib 100 mg twice daily.

Other dosing schedules and ramp-up periods may be explored by protocol amendment under advisement of the SRC.

All participants will be followed for survival until death, loss to follow-up, the Sponsor closes study or withdrawal of consent, whichever occurs first.

In **Module 2**, participants with r/r MCL will be administered AZD4573 as monotherapy and in combination with acalabrutinib 100 mg twice daily.

Part A will have 2 dosing periods. Period 1 will explore once-weekly IV administration of AZD4573 12 mg monotherapy (with intra-patient ramp up) in 2 cycles. The AZD4573 12 mg dose to be administered in Period 1, Cycles 1 and 2, is the established RP2D in DLBCL determined in the FTIH study (Study D8230C00001).

Period 2 will assess the safety and tolerability of combination therapy of AZD4573 with acalabrutinib 100 mg twice daily. The dose of AZD4573 in combination with acalabrutinib will be the RP2D determined in Module 1 Part A. Treatment with AZD4573 combination therapy may be continued until disease progression, an unacceptable drug-related toxicity occurs, or the participant withdraws or is withdrawn from the study as defined in the protocol.

All participants will be followed for survival until death, loss to follow-up, the Sponsor closes the study, or withdrawal of consent, whichever occurs first.

Data Monitoring Committee: No

Statistical Methods: Refer to the individual study modules for the statistical considerations in this study.

1.2 Schema

Refer to individual study modules for study schema.

1.3 Schedule of Activities

Refer to individual study modules for schedule of activities (SoA).

2 INTRODUCTION - CORE

2.1 Study Rationale

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

The mechanism of action of AZD4573 and in vivo data in nonclinical models suggest the potential to combine it with a number of other anti-cancer treatments, resulting in either synergistic or additive activity (see Section 4.1). The modular study design allows an investigation of optimal combination doses of AZD4573 with other anti-cancer treatments.

The study will consist of one or more modules, each evaluating the safety, tolerability, and efficacy of AZD4573 in combination with one or more other anti-cancer agents. Further modules will be added via protocol amendment. Study information applicable to all participants in this study will be described in the core protocol; each specific study treatment will be described in a separate module.

There are two parts to each combination module of this study:

- Part A: Phase I dose setting to assess safety and tolerability and determine or confirm dose(s) and schedule(s) of each combination treatment to be evaluated in Part B.
- Part B: Phase II cohort expansions in select participant groups to assess preliminary anti-tumour efficacy of each combination treatment.

Initiation of Part B for each module will depend on the evaluation of safety outcomes in Part A. The addition of new modules will depend on evaluation of preclinical data showing a synergistic or additive effect of AD4573 in combination with other anti-cancer agents in the relevant disease model.

Additional modules and combinations of AZD4573 with other anti-cancer agents may be added in the future via protocol amendment (see Section 4.3).

The results from this study will form the basis for decisions for future studies.

2.2 Background

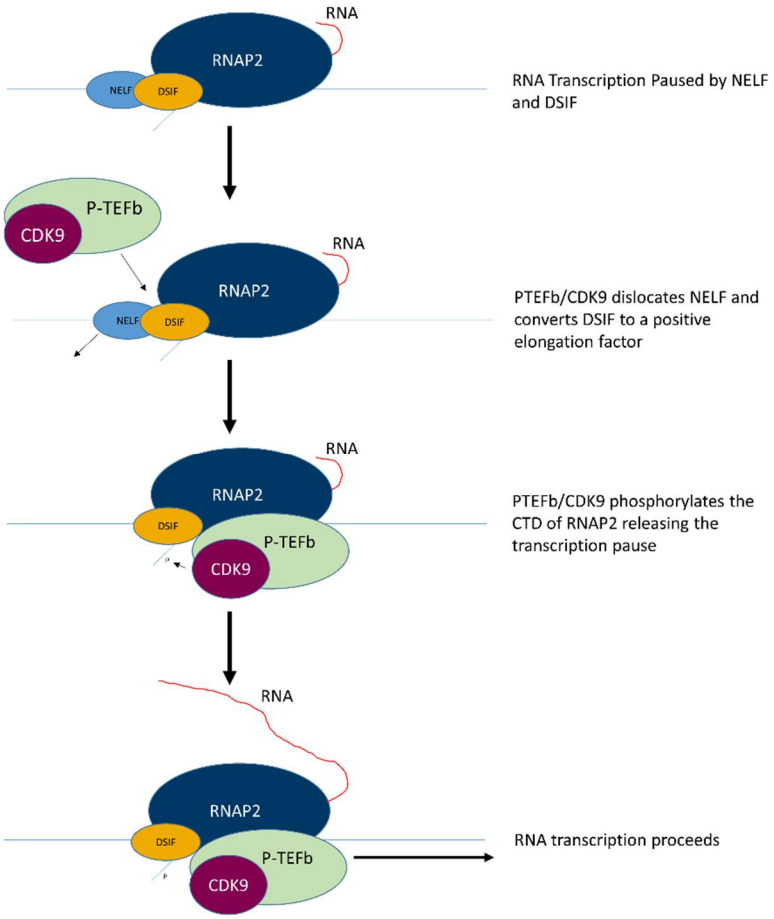
Background information for AZD4573 is included in this section. Refer to individual study modules for background information on the other anti-cancer agents being used in combination with AZD4573.

2.2.1 CDK9 and RNA Transcription Elongation

Cyclin-dependent kinases represent a family of closely related serine/threonine kinases that bind their cognate regulatory subunits, known as cyclins, to form active heterodimeric complexes. Several cyclin-dependent kinase (CDK)/cyclin complexes play crucial roles in regulating cell cycle progression (CDK1, 2, 4, 6), however, more recently they have also been implicated in transcription and mRNA processing (CDK7, 8, 9, 12, 13) (Lue et al 2020, Lim and Kaldis 2013, Malumbres 2014).

Regulation of transcription is a complex process governed in part through activity of CDK9 (Bywater et al 2013, Khoury et al 2003, Krystof et al 2012, Morales and Giordano 2016). Following successful transcription initiation, RNAP2 pauses downstream of the transcription start site, which serves as a checkpoint and allows for the rapid, synchronous activation of genes and integration of multiple regulatory signals before proper elongation can proceed (Gilchrist et al 2010, Adelman and Lis 2012). To release RNAP2 from this pause and permit subsequent elongation, multiple CDK9-mediated phosphorylation events are required. CDK9 forms the catalytic unit of the positive transcription elongation factor b (P-TEFb) (Bywater et al 2013). P-TEFb phosphorylates the elongation repressive complex made up of 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole-sensitivity-inducing factor (DSIF) and the negative elongation factor (NELF) resulting in the dissociation of NELF from RNAP2 and conversion of DSIF to a positive elongation factor. P-TEFb also phosphorylates the carboxyl-terminus domain (CTD) of RNAP2, which is comprised of 52 heptapeptide repeats (YSPTSPS), at the Ser2 position in the final step before elongation can proceed (Sanso and Fisher 2013).

Figure 1 CDK9 and RNA Transcription



2.2.2 CDK9 and Cancer

As an integral node of the transcription regulatory network, CDK9 represents a potential target for cancer therapy. Short-term inhibition of CDK9 results in transient transcriptional repression and rapid downregulation of genes with short-lived mRNAs and labile proteins (Boiko et al 2020). This provides therefore a therapeutic opportunity to treat tumours preferentially dependent on target key driver oncogenes fitting that profile without having broad toxicity related to general transcriptional repression. Two such genes are *MCL-1* and MYC (Yang et al 1996, Stewart et al 2010, Hann and Eisenman 1984). *MCL-1* is an anti-apoptotic BCL2 family member, and its amplification and overexpression have been linked to increased survival of and chemotherapy resistance in various cancers (Beroukhim et al 2010, Baiocchi et al 2010, Balko et al 2014, Gomez-Bougie et al 2007, Glaser et al 2012). MYC is a proto-oncogenic transcription factor that coordinates diverse transcription programs and is overexpressed through amplification or genomic rearrangement in multiple indications (Beroukhim et al 2010, Ciriello et al 2013). Given the pivotal role played by *MCL-1* and MYC in tumour cell growth and survival and tumour maintenance,

depletion of these oncoproteins in specific tumour contexts results in rapid cell death and tumour regressions (Glaser et al 2012, Silkenstedt et al 2021, Soucek et al 2013). CDK9 therefore represents an intriguing target to indirectly and transiently modulate these oncoproteins through transcription regulation to drive oncogene-addicted tumour cells toward cell death while sparing normal cells and tissues not dependent on these and other short half-life pro-tumour survival proteins.

2.2.3 Targeting CDK9

Several multi-CDK inhibitors have been progressed in clinical trials, including dinaciclib, which has CDK9 activity that reduced levels of MCL-1 in r/r CLL patients and demonstrated clinical activity attributed to CDK9 inhibition (Noy et al 2017, Parry et al 2010, Flynn et al 2015, Kumar et al 2015, Gojo et al 2013, Varadarajan et al 2015, Rahaman et al 2016). However, a more potent and selective CDK9 inhibitor, along with the appropriate PK for tuneable target engagement and an optimal dose/schedule leading to improved efficacy and/or therapeutic index is warranted.

2.2.4 AZD4573 and CDK9

AZD4573 (formerly known as AZ13810325) is a potent and selective inhibitor of CDK9 with nanomolar potency against the enzyme (IC50 < 4 nM) and excellent selectivity over other CDK family members. AZD4573 decreases pSer2RNAP2 levels. This decrease in pSer2RNAP2 is linked to preferential reduction of labile proteins like the BCL2 family anti-apoptotics Mcl-1 and Bfl-1 as well as other well-known oncoproteins like MYC, which leads to rapid induction of apoptosis in a broad range of human cancer cell lines derived from haematological malignancies (Cidado et al 2020, Boiko et al 2020).

AZD4573 demonstrates significant anti-tumour activity in vivo associated with transient CDK9 inhibition across a range of tumour xenograft models as a single agent when dosed intermittently. For example, durable tumour regressions can be achieved in the MV-4-11 acute myeloid leukaemia (AML) model with AZD4573 dosed on Day 1 and Day 2 weekly with 6 to 8 hours pSer2RNAP2 suppression on each day. Similar regressions are observed in the DLBCL tumour xenograft model, OCI-LY10, using both the aforementioned bi-weekly schedule as well as a once-weekly regimen, although responses are not as durable for the latter. AZD4573 also demonstrates improved depth and DoR when combined with a number of SoC or other targeted agents in vivo. For example, a combination of AZD4573 with rituximab in SUDHL-4 or with acalabrutinib in the OCI-LY10 model leads to significantly improved DoR post-completion of dosing as compared to each drug alone.

2.2.5 Nonclinical Information and Correlative Studies

2.2.5.1 Primary, Secondary and Safety Pharmacology

This section summarises the nonclinical primary, secondary, and safety pharmacology of AZD4573. The key findings are summarised below:

- AZD4573 is a potent inhibitor of CDK9 as measured in enzyme assays (IC_{50} < 4.0 nM), with > 5.8-fold selectivity for CDK9 over other CDKs and > 47.0-fold over other kinases. The mode of inhibition of AZD4573 was determined to be consistent with an adenosine triphosphate competitive inhibitor with rapid association (fast on) and fast intermediate dissociation kinetics.
- AZD4573 induced time- and dose-dependent reduction in phosphorylation of the CDK9 substrate RNAP2 at serine 2 in cells with an IC_{50} of 13.4 nM with selectivity over other CDK substrates. Loss of pSer2RNAP2 levels was associated with loss of Mcl-1 and MYC mRNA and MCL-1 and c-Myc protein levels (but not BCL2 and B-cell lymphoma extra-large [BCL-XL]) and subsequent caspase activation in MCL-1-dependent MV-4-11 cells within 6 hours. Six to 8 hours treatment was sufficient to induce maximal caspase activation and loss of cell viability in this cell line.
- AZD4573 rapidly induced dose-dependent apoptosis and loss of viability in a broad range of human cancer cell lines in vitro, particularly subtypes of AML, multiple myeloma (MM) and non-Hodgkin lymphoma (NHL) cell lines.
- AZD4573 demonstrated time- and dose-dependent transient modulation of pSer2RNAP2 and Mcl-1 and c-Myc protein levels leading to rapid induction of apoptosis in vivo that correlated with anti-tumour response in the MV-4-11 xenograft model. Almost complete regressions were observed in multiple studies when AZD4573 was dosed at 15 mg/kg twice daily with a 2-hour split dose on Day 1 and Day 2 every 7 days. Additionally, AZD4573 dosed once weekly in the OCI-LY10 xenograft model resulted in regressions although the DoR was shorter compared to the twice daily schedule. Consistent with in vitro data, AZD4573 also demonstrated anti-tumour activity as monotherapy with intermittent dosing in multiple additional human xenograft cancer models in vivo. Significant anti-tumour activity or regressions were observed in several models of AML, NHL and MM when dosed at 15 mg/kg twice daily on Day 1 and Day 2 every 7 days. Doses were well tolerated and without significant body weight loss.

AZD4573 also demonstrated good ability to combine with multiple agents in vivo improving efficacy. Combination of AZD4573 with Cytarabine prolonged durability of response in an AML xenograft model. Combination of AZD4573 with the BTK inhibitor acalabrutinib also resulted in more durable responses in an ABC DLBCL xenograft model using either the twice-daily or once-weekly schedule. Inhibition of the BTK pathway with acalabrutinib

causes an increase of certain BCL2 family pro-apoptotic proteins, like Bim (Deng 2017a, Deng et al 2017b, Sasi et al 2019), pushing the cancer cells closer to their apoptotic threshold, a mechanism known as 'apoptotic priming' (NCCN 2021, Ni Chonghaile et al 2011).

With the addition of AZD4573 following a short lead-in of acalabrutinib, both the magnitude and duration of anti-tumour response is increased compared to either monotherapy as evidenced by more rapid and robust cleavage of caspase-3 and delayed time to tumour regrowth following treatment cessation (Patent WO2019/058348; data on file, Astra Zeneca). Combination of AZD4573 with the anti-CD20 monoclonal antibody rituximab, a rituximab and chemotherapy combination therapy (RCHOP) or the BCL2 inhibitor venetoclax improved anti-tumour activity leading to complete regressions and highly durable responses in a GCB DLBCL model. Prolonged DoR to AZD4573 while still on treatment was observed in a MM model when combined with bortezomib. All combinations were well tolerated.

- In a secondary pharmacodynamic screen of 189 molecular targets, AZD4573 had activity (a defined IC_{50} value) against 10 targets within 100-fold of the CDK9 cell-based IC_{50}. When tested in the same panel, two pharmacologically active metabolites, AZ13830647 and AZ13848532, had a profile qualitatively similar to that of AZD4573, but with lower absolute potencies across the targets.
- AZD4573, AZ13830647 and AZ13848532 showed no activity (a defined IC_{50} value) in a panel of cardiac ion channels (including human Ether-à-go-go-Related Gene [hERG]) when tested up to 33 μM.
- In an anaesthetised rat study, a 1-hour IV infusion of 6.0 and 18.0 mg/kg AZD4573 was associated with a dose-dependent increase in heart rate (up to 27%). Concomitant with the increase in heart rate, a small transient decrease in the QA interval of up to 16% (indicating an increase in left ventricular contractility) was observed at 18.0 mg/kg. Recovery during the washout period was evident for both parameters affected. The lowest effect level for effects on the rat cardiovascular system was an AZD4573 free plasma concentration of 1250.0 nM at the end of the 6.0 mg/kg infusion.
- In a cynomolgus monkey telemetry study, a 2-hour IV infusion of AZD4573 had no effects on the cardiovascular system when tested up to the MTD of 1.25 mg/kg previously determined in a toxicology study (AZD4573 free plasma concentration at the end of the infusion of 75.0 nM).
- A 2-hour IV infusion of AZD4573 had no effects on the nervous or respiratory systems in rats, when tested in modified Irwin and whole-body plethysmography studies, up to 10.0 mg/kg (AZD4573 plasma free maximum concentration [C_{max}] of 445.0 nM, inferred from rat toxicology studies).

The results from these pharmacological studies support the use of AZD4573 in the proposed clinical trial.

CCI [redacted]

2.2.5.2 Good Laboratory Practice 1-Month Toxicology Studies (Rat and Monkey)

The toxicology of AZD4573 has been evaluated in repeat dose cycle IV infusion studies of up to 1-month duration in rats and cynomolgus monkeys. A non-Good Laboratory Practice (GLP) in vitro genotoxicity study was also conducted.

Key findings from these studies are summarised below:

- Dose-related decreases in peripheral white blood cell parameters, particularly neutrophils or lymphocytes, were noted in the rat and cynomolgus monkey following repeated dose cycle administration of AZD4573. The DLT in the rat was severe neutropenia with resulting disseminated bacterial colonies in several tissues. These white blood cell decreases were related to the primary pharmacological action of AZD4573 and showed evidence of partial recovery between dose cycles and at the end of the 16-day recovery period.
- The principal histopathological finding in the 1-month repeat dose cycle toxicology studies was dose-dependent decreased cellularity of lymphoid tissues and bone marrow, which are consistent with the primary pharmacological action of AZD4573. Decreased cellularity was seen in the thymus, spleen, and lymph nodes of rats and cynomolgus monkeys, and in the bone marrow and Peyer's patch of rats only. Reversibility of the bone marrow findings was seen at the end of the 16-day recovery period, but mild decreases in lymphoid tissue cellularity were still present in both species at the end of the recovery period.
- Repeated dosing of AZD4573 to the cynomolgus monkey was associated with dose-limiting emesis and diarrhoea at 1.0 mg/kg and above. No test article-related histopathological changes were seen in the gastrointestinal tract in the monkey dose range finding and 1-month studies.
- Exocrine pancreatic acinar cell atrophy and/or vacuolation were seen at $\geq$ 0.5 mg/kg in the cynomolgus monkey 1-month toxicology study. In the rat, repeat dosing of AZD4573 showed vascular fibrinoid necrosis, interstitial oedema, fibrino-haemorrhagic inflammation or acinar cell apoptosis in the pancreas at $\geq$ 8.0 mg/kg. Transient increases in amylase and lipase correlated with the observed histopathological changes. Reversibility was noted at the end of the 16-day recovery period in the rat, but mild acinar cell atrophy was still present in the monkey.

- Mucosal or villous atrophy with mucosal oedema were observed in the small and large intestine at ≥ 6.0 mg/kg in the 1-month rat toxicology study. Reversibility of the intestinal findings was noted at the end of the 16-day recovery period.
- Cortical necrosis of the adrenal glands was observed in the rat at ≥ 6.0 mg/kg following repeated dosing in the 1-month toxicology study and showed reversibility at the end of the 16-day recovery period.
- Femoro-tibial epiphyseal growth plate dysplasia was present in cynomolgus monkeys at ≥ 0.5 mg/kg in the 1-month repeat dose toxicology study and showed reversibility at the end of the 16-day recovery period.
- Histopathological findings were noted in the kidneys of rats (tubular necrosis and dilatation) at a non-tolerated dose of 12.0 mg/kg and in the monkey (tubular basophilia and dilatation) at 1.0 mg/kg and above in the dose range finding studies. There were no test article-related histopathological changes in the kidneys of rats or monkeys in the 1-month toxicology studies following dosing up to 8.0 mg/kg or 1.25/1.0 mg/kg, respectively.
- Dosing procedure-related haemorrhage, erosion, ulceration or mixed cell infiltration were evident at the rat administration and monkey extravascular tolerance sites on the one-month toxicology studies. Reversibility of the extravascular tolerance site findings were seen at the end of the 16-day recovery period, but the rat administration site changes were still present.
- AZD4573 was non-mutagenic in a non-GLP Ames test.
- AZD4573 showed no evidence of phototoxic potential in a Balb/c 3T3 mouse fibroblast assay when conducted in the presence and absence of ultraviolet light.

The results from these toxicology studies support clinical trials with AZD4573 in patients with advanced cancer.

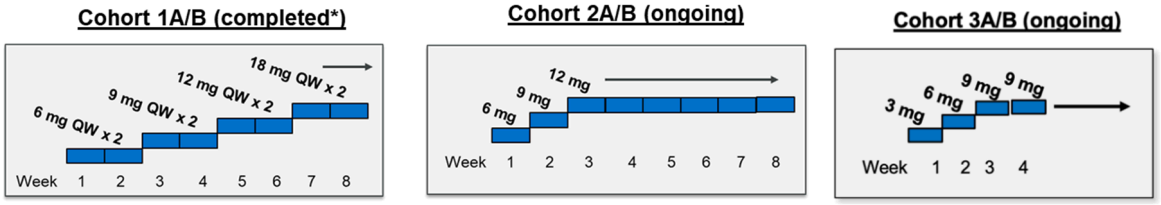
CCI [redacted]

2.2.6 Clinical Experience with AZD4573

A FTIH, multicentre, Phase I dose-escalation study (D8230C00001) including an intra-patient ramp up is currently being conducted with AZD4573 monotherapy in participants with r/r haematological malignancies. Two parallel arms of the study (A and B) are composed of separate cohorts of participants at different target dose levels (9, 12, and 18 mg). Arm A includes participants with r/r haematological malignancies (all comers, excluding AML, acute lymphocytic leukaemia [ALL], high risk myelodysplastic syndromes [MDS], chronic myelomonocytic leukaemia [CMML], CLL, and Richter's syndrome). Arm B includes participants with r/r haematological malignancies, including but not limited to AML, ALL,

high-risk MDS, CMML, CLL, and Richter's syndrome. CCI summarises in greater detail the results from the first 38 participants (number of participants: Cohort 1 Arm A = 9, Cohort 1 Arm B = 5, Cohort 2 Arm A = 11, Cohort 2 Arm B = 8, Cohort 3 Arm A = 1, Cohort 3 Arm B = 4) treated at 18 mg and 12 mg target doses. A diagram of the previous and now ongoing cohorts treated is presented in Figure 2.

Figure 2 Schematic of Study D8230C00001



Abbreviation: QW = once weekly.

With respect to safety, 35 of 38 participants (92.1%) had ≥ 1 Common Terminology Criteria for Adverse Events (CTCAE) treatment-emergent adverse event (TEAE) of Grade ≥ 3. The most frequently reported CTCAE Grade 3/4 TEAEs (≥ 20% of participants overall) were: tumour lysis syndrome (TLS; 16 participants, 42.1%); neutropenia (14 participants, 36.8%); anaemia (9 participants, 23.7%).

The most common TEAEs identified as DLTs in 9 participants included TLS (3 participants), thrombocytopenia (1), transaminase or gamma-glutamyl transferase (GGT) elevations (4) and hypotension (1). The last event was regarded as potentially related to inadequate hydration during TLS prophylaxis.

Preliminary efficacy data from the first 30 participants is summarised in Table 1.

Table 1 Preliminary Efficacy Data – Best Overall Response Rate by Cohort (Study D8230C00001)

	Cohort 1 (AZD4573 18 mg) n (%)		Cohort 2 (AZD4573 12 mg) n (%)		Cohort 3 (AZD4573 9 mg) n (%)		Total (N=30) n (%)
	Arm A (N = 9)	Arm B (N = 5)	Arm A (N = 11)	Arm B (N = 8)	Arm A (N = 1)	Arm B (N = 4)	
Best overall response							
CR	1 (11.1)	0	0	0	0	0	1 (2.6)
PR	0	0	1 (9.1)	0	0	0	1 (2.6)

	Cohort 1 (AZD4573 18 mg) n (%)		Cohort 2 (AZD4573 12 mg) n (%)		Cohort 3 (AZD4573 9 mg) n (%)		Total (N=30) n (%)
	Arm A (N = 9)	Arm B (N = 5)	Arm A (N = 11)	Arm B (N = 8)	Arm A (N = 1)	Arm B (N = 4)	
SD	3 (33.3)	1 (20.0)	3 (27.3)	1 (12.5)	0	0	8 (21.1)
PD	4 (44.4)	1 (20.0)	4 (36.4)	4 (50.0)	0	1 (25.0)	14 (36.8)
NA/Unknown	1 (11.1)	3 (60.0)	3 (27.3)	3 (37.5)	1 (100)	2 (50.0)	13 (34.2)
Objective response rate	1 (11.1)	0	1 (9.1)	0	0	1 (25.0)	3 (7.9)
95% CI	(0.3, 48.3)	(0, 52.2)	(0.2, 41.3)	(0, 36.9)	(0, 97.5)	(0.6, 80.6)	(1.7, 21.41)

CCI

Response assessments are per Investigator by standardised response criteria for the applicable indication (eg, Cheson criteria for DLBCL, Döhner criteria for AML).
Abbreviations: AML = acute myeloid leukaemia; CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; NA = not available; PD = progressive disease; PR = partial response; SD = stable disease.

Overall, best overall responses (based on disease assessments at the protocol-defined 2 month assessment time point) included one with CR, one with PR, 8 with stable disease (SD), and 12 with progressive disease (PD):

- Of the participants with DLBCL (n = 17), there was one with CR, one with PR, 4 with SD, 7 with PD, and 4 with unknown response. Among these, one with SD and one with a CR experienced CTCAE Grade3 TLS. Responses were observed in participants whose tumour cell of origin was GCB and non-GCB.

In addition, signs of clinical activity were observed in participants with DLBCL and CLL as short, repeated tumour size reductions after each AZD4573 administration of up to 49% of the tumour volume, but with tumour regrowth during off-treatment periods. This pattern was observed over a range of dose levels and points to the need for combination therapies directed to sustaining the potential clinical benefit with AZD4573 treatment.

Evidence of clinical activity was also observed in participants with other haematological malignancies, including CLL, AML, and MM. For example, one participant with MM previously treated with two lines of therapy, exhibited SD and remained on AZD4573 treatment for 30 months, whereafter the participant went on to radiotherapy to treat a remaining plasmacytoma. Overall, among the first 38 participants with mixed haematological malignancies treated, 16 (42.1%) exhibited laboratory evidence of TLS. These data suggest

that efficacy and manageable safety may be achievable not just in DLBCL, but also in a range of other haematological diseases.

CCI [redacted]

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of AZD4573 may be found in CCI [redacted]

Refer to individual study modules for the benefit/risk assessment of other anti-cancer agents in combination with AZD4573.

2.3.1 Risk Assessment

Based on nonclinical toxicology findings and clinical experience to date, including experience from other medicinal products in the same class, the following have been assessed as risks for AZD4573:

Important identified risks:

- Tumour lysis syndrome
- Transaminases increase
- Bilirubin increase with transaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST], or both ALT and AST) increase
- Diarrhoea
- Nausea
- Vomiting
- Neutropenia (includes neutrophil count decreased)
- Febrile neutropenia

Important potential risks:

- Gastrointestinal toxicity
- Infection/Bone marrow toxicity with peripheral effect/lymphoid tissue hypocellularity
- Liver injury
- Neutropenic sepsis

Potential risks for AZD4573 include:

- Pancreatic injury
- Cortical adrenal injury
- Drug-drug interactions
- Myocardial ischaemia
- Heart rate increase

For a complete characterisation for each risk please refer to CCI [redacted]

In general, the protocol includes frequent monitoring of blood counts and clinical chemistry, along with additional safety monitoring. A urine dipstick test will also be performed, where a positive test will trigger urine microanalysis to exclude casts (red cell and protein casts). For a summary of management for each risk please refer to the individual study modules. Dose modifications for management of AZD4573 toxicities are also provided in the individual study module.

In addition to these risks, Embryo-foetal and Reproductive toxicity is Missing information in relation to AZD4573.

No reproductive toxicology nor teratogenic studies have been conducted with AZD4573 to date, and it is unknown whether the drug is excreted in human milk. Therefore, women of childbearing potential and men should agree to use highly-effective contraception as specified in Section 5.3, and women who are breastfeeding are excluded from the study. Women and men should be fully informed of the lack of reproductive toxicity testing, and women must have a negative serum pregnancy test at Screening, and a negative serum or urine pregnancy before receiving investigational product (IP).

AstraZeneca has procedures in place to ensure that new or emerging, important clinical safety findings are handled in accordance with a globally consistent process. This guarantees that AstraZeneca's safety reporting obligations to Regulatory Authorities, investigators, and Ethics Committees are met and optimal risk management of participants is maintained. These procedures have been developed to be consistent with 'International Council for Harmonisation (ICH) E2A Clinical Safety Data Management: Definitions and standards for reporting,' which provides guidance to support that suspected unexpected serious adverse reaction (SUSAR) information must be provided as early as possible, but no later than 15 days after the Sponsor becomes aware that the case meets the minimum criteria for expedited reporting.

Clinical safety findings may arise during or after a participant has completed the study, including but not limited to individual case reports. Important new clinical safety findings are those findings that might adversely influence the benefit/risk assessment of a medicinal product. Upon review of a specific clinical safety finding, AstraZeneca may make a decision to communicate the analysis of a safety finding in an expedited manner, so that investigators can appropriately manage participants accordingly and ensure that there remains a positive risk-benefit analysis.

The majority of adverse events (AEs) observed with the clinical use of AZD4573 to date have been gastrointestinal (nausea, vomiting, and diarrhoea), haematological (neutropenia, febrile neutropenia, and thrombocytopenia), hepatic (transaminase increase with or without concomitant bilirubin increase), and TLS. These events have been manageable with appropriate prophylaxis and treatment, and by dose modification.

During the 3-week dose ramp up in the FTIH study (D8230C00001) in DLBCL participants, one event of clinical TLS was seen. The abnormal TLS laboratory results were detected at 6 hours after the start of the infusion. Based on these data, if, in the current study, a participant has no signs of laboratory or clinical TLS at the 6-hour TLS monitoring assessment, the participant may leave the clinic after the collection of other laboratory samples, as per the SoA, at 7 hours after the start of the infusion and managed as an outpatient, at the discretion of the Investigator. These participants must return to the clinic the next morning to complete the 24 hour TLS monitoring period as per the SoA (Cycle 1 Weeks 1-3). Participants showing signs of laboratory or clinical TLS at 6 hours after the start of the infusion must be admitted for in-patient TLS monitoring for a minimum of 24 hours after the start of the infusion and monitored every 4 to 6 hours during this time (or more frequently if clinically indicated). Sites retain the option to hospitalise participants based on clinical judgement, despite normal TLS laboratory results 6 hours after the start of the infusion.

Regarding the hepatic toxicity events encountered to date with AZD4573, it has been observed that while the biochemical changes of increased transaminase with concomitant elevation in bilirubin seen in some participants could be classified as Hy's Law by its strict definition, they do not follow a pattern that is consistent with true Hy's Law predictive of hepatic injury. The events are rapidly resolved and to date have not led to any clinical sequelae or lasting hepatic injury. Repeated dosing with AZD4573 following these events has demonstrated that there is no consistent pattern of recurrence and no consistent increase in severity of the events if they do recur.

2.3.2 Benefit Assessment

AZD4573 may have the potential to provide clinical benefit in terms of anti-tumour activity, as monotherapy and in combination with other anti-cancer treatments, in patients with a

variety of r/r haematological malignancies who have exhausted, or cannot tolerate, SoC options.

Preliminary anti-tumour activity has been observed with AZD4573 as monotherapy in participants with r/r haematological malignancies in the ongoing Phase I, FTIH, dose-escalation study (D8230C00001; see Section 2.2.6). Best overall responses included one CR, one PR, and 4 SD in participants with DLBCL and evidence of clinical activity was observed in participants with other haematological malignancies, such as CLL, AML, and MM.

Please refer to the individual study modules for the benefit/risk assessments for each combination treatment.

2.3.3 Overall Benefit/Risk Conclusion

Considering the measures in place to minimise risks with AZD4573 in participants of this Phase I/II study (including safety monitoring and dose modification criteria specified in the protocol for cases of transaminase ± bilirubin increase) and the observed clinical responses and SD in a r/r participant population with AZD4573 monotherapy, the Sponsor believes the anticipated benefits that may be afforded to participants with r/r haematological malignancies currently outweigh the identified and potential risks associated with AZD4573.

As outlined in Section 2.2.6, AZD4573 has shown activity in the ongoing FTIH study (D8230C00001). The results of nonclinical studies with AZD4573 in combination with other anti-cancer agents demonstrate an increase in both the magnitude and duration of anti-tumour response compared with single agents alone (Section 2.2.5.1). Therefore, therapy with AZD4573 in combination with other anti-cancer agents may reasonably be expected to yield greater clinical benefit than with AZD4573 alone.

Please refer to the individual study modules for the benefit/risk assessments for each combination treatment.

Please refer to Appendix A 11 for the benefit/risk assessment pertaining to the conduct of this study during the COVID-19 pandemic.

3 OBJECTIVES AND ENDPOINTS – CORE

Refer to the individual study modules of the protocol for detailed objectives and endpoints.

Objectives	Endpoints
Primary	
Part A	

Objectives	Endpoints
• Assess the safety and tolerability, describe the DLTs, and identify the MTD and/or RP2D of AZD4573 when administered intravenously to participants with advanced relapsed/refractory haematological malignancies, in novel combinations with other anti-cancer agents[a]	• Adverse events, laboratory data, vital signs, and ECG changes
Part B	
• Assess the efficacy of AZD4573 in novel combinations with other anti-cancer agents in participants with relapsed/refractory haematological malignancies	• Refer to Modules for endpoints
Secondary	
Part A and B	
• Assess the plasma/serum PK of AZD4573 and other anti-cancer agents when given in combination	• Plasma concentrations and derived PK parameters for AZD4573 summarised by cohort and dose level for the PK analysis set • Plasma/serum concentrations and derived PK parameters for other anti-cancer agents summarised by cohort and dose level for the PK analysis set
Part B	
• Further assess efficacy of AZD4573 in novel combinations with other anti-cancer agents	• Refer to Modules for endpoints
• Assess the safety and tolerability of the RP2D of AZD4573 in novel combinations with other anti-cancer agents	• Adverse events, laboratory data, vital signs, and ECG changes
Exploratory	
Part A	
• Assess the efficacy of AZD4573 in novel combinations with other anti-cancer agents in participants with relapsed refractory haematological malignancies	• Refer to Modules for endpoints

Objectives	Endpoints
Part A and B	
• Assess the PD of AZD4573 CCI [redacted]	• CCI [redacted]
• Assess CCI [redacted]	• CCI [redacted]
• To CCI [redacted]	• CCI [redacted]

[a] If the MTD and RP2D have been set in a given disease population, the dose setting phase can be a dose confirmation phase.

Abbreviations: DLT = dose-limiting toxicity; ECG = electrocardiogram; MTD = maximum tolerated dose; PK = pharmacokinetics; RP2D = recommended Phase II dose.

CCI [redacted]

4 STUDY DESIGN - CORE

4.1 Overall Design

In accordance with AstraZeneca standard procedures this clinical study protocol (CSP) has been subject to a full peer review.

This is a modular, multicentre, open-label, non-randomised, Phase I/II, dose setting and expansion study including an intra-patient dose ramp up.

AZD4573 will be administered intravenously in novel combinations with anti-cancer agents, to participants with r/r haematological malignancies.

Module 1 comprises AZD4573 combined with acalabrutinib in participants with r/r DLBCL or r/r MZL.

Module 2 Part A is a window study comprising AZD4573 monotherapy followed by AZD4573 + acalabrutinib combination treatment in participants with r/r MCL.

Inclusion of further modules via protocol amendments will be based on emerging preclinical data (eg, showing a synergistic or additive effect of AZD4573 with the proposed anti-cancer therapy) and emerging safety and tolerability data from previous modules.

Other modules studying AZD4573 in combination with other anti-cancer therapies for treatment of advanced haematological malignancies may include, but are not restricted to:

- Combination of AZD4573 with acalabrutinib and rituximab
- Combination of AZD4573 with venetoclax
- Combination of AZD4573 with bendamustine and rituximab
- Combination of AZD4573 with gemcitabine and oxaliplatin
- Combination of AZD4573 with azacytidine

A study-specific SRC (including at a minimum the Sponsor Medical Monitor and participating investigators who have enrolled participants), in accordance with its charter, will be responsible for providing ongoing safety surveillance of the study, with regularly scheduled reviews of safety, PK, and other relevant data. This committee will be responsible for making recommendations for dose escalation or dose de-escalation decisions, including recommendations on opening cohorts for backfill, as well as making recommendations regarding further conduct of the study. This committee may also meet to review data at other time points (eg, in response to AEs assessed as medically relevant by the Medical Monitor). The SRC will review available clinical and laboratory safety data and other relevant data prior

to making recommendations. All SRC recommendations will be documented and shared in writing with all participating sites in accordance with its charter.

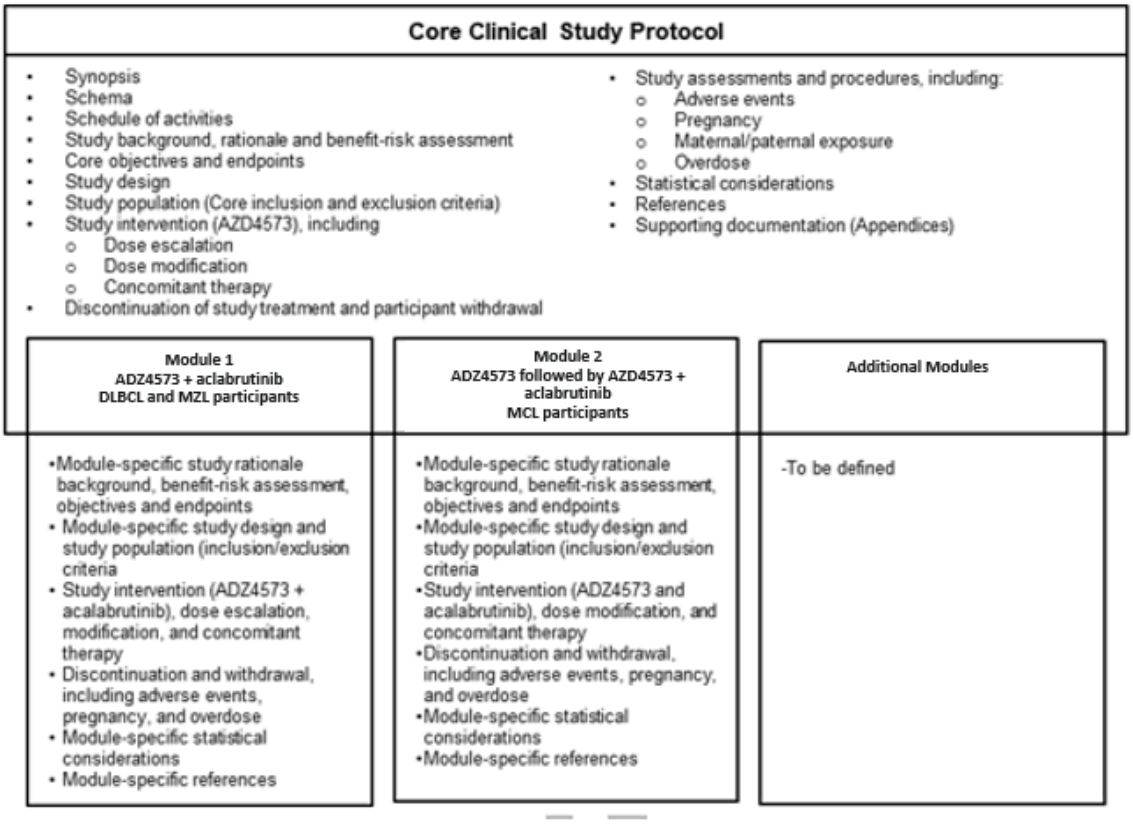
The initial dosing schedule of AZD4573 in each module may be subsequently changed between participant cohorts, in response to emerging safety, PK, and PD findings.

The structure of the study protocol is illustrated in Figure 3, where the protocol core contains elements common to all modules and then one or more modules containing the specific details relevant to that module.

Assignment of participants to receive study treatment in a given study module will be based on meeting inclusion/exclusion criteria and available slots. Guidelines for participant allocation when multiple study cohorts are open will be provided separately in the Patient Enrolment Guidelines. There are no control groups, other than historical data, in any of the study cohorts.

Since Study D8230C00002 was first opened (in July 2020) significant challenges have occurred with recruitment into both Module 1 and Module 2. These challenges precluded completion enrolment within the allocated time frame of January 2023. AstraZeneca has therefore taken the decision to stop recruitment into the study. Based on this decision, the main purpose of this protocol amendment is to add a rationale for the proposed reduction in scope of study D8230C00002 and to set out measures to allow patients still receiving clinical benefit of the study treatment after data collection for the primary analysis has completed to continue study treatment. End of study definitions and scope of data collection are updated to describe this scenario

Figure 3 Modular Protocol Design



The population of participants to be included in Part A of each module will be defined in the respective module.

Part A of each module will identify the MTD and/or RP2D of AZD4573 in combination with other anti-cancer agents. The initial target dose of AZD4573 selected for this study in combination with other anti-cancer agents will be attained by an intra-patient ramp up during the first cycle of treatment. If the MTD and RP2D have already been set in another disease population, the dose setting phase can be a dose confirmation phase.

During dose setting, a recommendation about the dose level for each next cohort of evaluable participants will be made by the SRC, guided by decision rules provided in study modules. In Module 1, the decision rules are based on a modified toxicity probability interval (mTPI-2) design (Guo et al 2017) with a 30% target DLT rate (± 5%) for MTD: dose escalation, stay at the current dose, de-escalation, or de-escalation and current dose is unsafe so will never be used again due to unacceptable toxicity.

Part B cohort expansions of specific participant groups will be defined in the respective modules.

After determining the RP2D in Part A (dose setting), separate expansion cohorts for participant subgroups may be opened in Part B in order to further assess safety and tolerability and explore anti-tumour activity of particular drug combinations.

Cycle 1 may also include the intra-patient ramp-up. Participants in relevant subgroups who are treated at the RP2D dose level in Part A will contribute to primary analyses along with participants from Part B.

During the 3-week dose ramp-up in the FTIH study (D8230C00001) in DLBCL participants, one event of clinical TLS was seen. The abnormal TLS laboratory results were detected at 6 hours after the start of the infusion. Based on these data, if, in the current study, a participant has no signs of laboratory TLS or clinical TLS at the 6-hour TLS monitoring assessment, the participant may leave the clinic after the collection of other laboratory samples, as per the SoA, at 7 hours after the start of the infusion and managed as an outpatient, at the discretion of the Investigator. These participants are not required to be hospitalised overnight, and must return to the clinic the next morning to complete the 24-hour TLS monitoring period as per SoA (Cycle 1 Weeks 1-3).

During the intra-patient ramp-up phase (Cycle 1, Week 1-Week 3), overnight hospitalisation is required-for participants showing signs of laboratory or clinical TLS at 6 hours after the start of the infusion must be admitted for in-patient TLS monitoring for a minimum of 24 hours after the start of the infusion and monitored every 4 to 6 hours during this time (or more frequently if clinically indicated). Sites retain the option to hospitalise participants based on clinical judgement, despite normal TLS laboratory results 6 hours after the start of the infusion.

Admission for further AZD4573 administrations is strongly recommended for participants who have experienced TLS events during the ramp-up phase. Participants who have previously experienced TLS should be admitted the night before each AZD4573 dose for TLS prophylaxis. Please refer to each study module for prophylaxis and management of TLS.

All participants will have haematology, chemistry, and urinalysis safety panels performed at Screening. Once dosing commences, all participants will be evaluated for safety, including clinical chemistry and haematology. If clinically indicated, additional clinical laboratory tests and evaluations are to be performed by the Investigator (eg, additional haematology/clinical chemistry panels, TLS parameters, liver enzyme tests); these need to be entered into the electronic case report form (eCRF).

4.2 Scientific Rationale for Study Design

This is a modular Phase I/II study evaluating the safety, tolerability, and clinical efficacy of AZD4573 in novel combinations with other anti-cancer agents in participants with r/r haematological malignancies who have failed prior standard therapy(ies) and for whom no other standard therapy is available.

Refer to individual modules for the rationale for the study design for each specific combination of AZD4573 with other anti-cancer agents.

Preliminary anti-tumour activity has been observed with AZD4573 as monotherapy in participants with r/r haematological malignancies in the ongoing Phase I, FTIH, dose-escalation study (D8230C00001; see Section 2.2.6). In addition, data with AZD4573 in combination with various other anti-cancer agents in nonclinical models have shown an increase in both the magnitude and duration of anti-tumour response compared with the single agents alone (see Section 2.2.5.1). This study is, therefore, modular in design, allowing evaluation of the safety, tolerability, PK, pharmacodynamics, and preliminary activity of AZD4573 in combination with different anti-cancer agents in participants with select r/r haematological malignancies.

This study will characterise the PK of AZD4573 and other anti-cancer agents when given in combination and explore CCI [redacted] by assessing pharmacodynamic/exploratory CCI [redacted], and CCI [redacted] The results from this study will form the basis for decisions for future clinical studies.

CCI [redacted]

CCI [redacted]

In conclusion, based on the data available to support preclinical activity of AZD4573 across a range of in vitro/in vivo models originating from cells from patients with haematological malignancies, coupled with clinical activity observed with other CDK9 inhibitors and preliminary safety and efficacy data available from the first 38 participants dosed with AZD4573 in the FTIH study (D8230C00001), it is felt that further investigation of AZD4573 is warranted given the high unmet need for treatment in the patient population chosen for this study.

4.3 Regulatory Amendment for Additional Modules

To support amendment of the protocol for additional modules, AstraZeneca will provide a summary of all nonclinical and clinical data to support the proposed new combination and dosing schedule; this will include updating the following:

- Study objectives
- Background information providing rationale for the proposed patient population(s) and the proposed treatment plan(s)
- Study eligibility criteria
- A detailed description of the proposed study treatment plans
- A revised schedule of participant assessments
- A summary of safety data from the completed or ongoing cohort(s)/modules(s) and the proposed toxicity management plans for the proposed new combination
- A description of any dose modifications and the data (clinical safety information, clinical PK data, and nonclinical data) that support the safety of the proposed dose modifications for the regimen in question
- A clearly stated sample size and justification for the proposed sample size based on the objectives for that specific cohort/module
- A detailed description of the method and performance characteristics of any test that will be used to identify the participant population to be enrolled in the cohort/module, if the population will be selected based on a diagnostic assay

4.3.1 Europe and Rest of World

AstraZeneca will provide a substantial amendment for review and approval.

4.3.2 United States of America

AstraZeneca will provide an amendment to the FDA 60 days in advance of planned enrolment into a new Module for any combination involving a drug for which the RP2D has not been determined for the proposed dosage regimen to be employed, or at least 30 days in advance of

a planned enrolment into a Module for drugs where the RP2D has been determined for the proposed dosage regimen to be employed.

4.4 Justification for Dose

Refer to individual modules for dose justification.

4.5 End of Study Definition

The end of module is defined as the last scheduled visit or contact of the last participant enrolled in the module.

The overall end of the study is defined as the date of the last visit of the last participant. In the event any participant remains on treatment following the end of the data collection for the primary analysis, the last visit of the study will be the date when the last participant permanently discontinued treatment with all investigational products. However, the database will be closed following end of data collection, and participants remaining on treatment will only be followed for SAEs. In all other aspects, the participant will receive SoC as per local practice.

Individual participants will normally be considered to have completed the study if they have had a 30-Day Safety Follow-up visit performed, or if the treating site has confirmed the SFU visit will not be performed. For participants continuing treatment after the data cut-off for the primary analysis the last visit of the study will be the date when the last participant permanently discontinued treatment with all investigational products.

Details of planned data analyses are provided in each of the study modules. The results from each module will be reported to Regulatory Authorities within one year of the end of the module.

Details on dissemination of clinical data are contained in Appendix A 6.

5 STUDY POPULATION - CORE

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

5.1 Inclusion Criteria – Core

NOTE: This study will be enrolling participants with haematological malignancies.

Each participant should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned to a study cohort. Under no circumstances can there be

exceptions to this rule. Participants who do not meet the entry requirements are screen failures, refer to Section 5.4.

Participants must meet the inclusion and exclusion criteria of both the core and the module protocol. Where there are differences in stringency or cut-off values, the specific module takes precedence. For example, if haematological medication parameters are stricter in the module than in the core, the Investigator should adhere to the module criteria.

Participants are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

Provision of signed and dated, written informed consent prior to any mandatory study-specific procedures, sampling, and analyses. Participants are also required to consent to the provision of any archival tumour biopsies, where applicable. For participants who consent, provision of signed and dated written genetic informed consent prior to collection of samples for genetic analysis.

Age

1 Participant must be ≥ 18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.

3 Must have received at least one prior line of therapy for the treatment of current disease and a clinical study is the best option for next treatment based on prior response and/or tolerability.

4 Documented active disease requiring treatment that is r/r defined as:

- Recurrence of disease after response to at least one prior line(s) of therapy

  or

- Progressive disease after completion of or on the treatment regimen preceding entry into the study or
- Disease that did not achieve an objective response (overall response of CR or PR).

5 Adequate haematological function (as defined in individual modules).

6 Adequate organ function at Screening as defined below in Table 2:

Table 2 Criteria for Adequate Organ Function

Category	Parameter	Value

Hepatic	Bilirubin	≤ 1.5 × ULN in the absence Gilbert's syndrome[a]
		≤ 3.0 × ULN if the participant has Gilbert's syndrome[a]
	Alanine transaminase and aspartate transaminase	< 3.0 × ULN
Renal	Calculated creatinine clearance by Cockcroft Gault equation [(140-Age) • Mass (kg)/(72 • creatinine mg/dL) • multiply by 0.85 if female])	≥ 60 mL/minute
Coagulation	INR	< 1.5 × ULN
Pancreatic	Lipase	≤ 3.0 × ULN and no ongoing pancreatitis
	Amylase	≤ 3.0 × ULN and no ongoing pancreatitis
Cardiac	LVEF as assessed by echocardiography MUGA[b]	≥ 40.0%

[a] Gilbert's syndrome = ratio between total and direct bilirubin > 5.

[b] Appropriate correction to be used, if a MUGA is performed.

Abbreviations: INR = International Normalised Ratio; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition scan; ULN = upper limit of normal.

7 Uric acid level < upper limit of normal (ULN). If hyperuricaemia is present at Screening, SoC therapy for hyperuricaemia should be administered (including IV fluid and rasburicase or allopurinol) to reduce the uric acid levels to < ULN before the start of study intervention.

8 Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules intact without difficulty, receiving IV administration of study drug and being admitted, when required, for up to 24 hours during study drug administration.

Sex

9 Male or female.

Reproduction

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Male participants must be willing to use barrier contraception (ie, condoms) and female partners should use highly-effective methods of contraception for the duration of the study and for a washout period of 4 months for men and 7 months for women after discontinuing AZD4573.

A more detailed description of the required lifestyle restrictions relating to reproduction is provided in Section 5.3.1.

10 Negative pregnancy test (serum) at Screening for female participants of childbearing potential.

11 Female participants should not be breastfeeding.

12 Female participants must be one year post-menopausal, surgically sterile, or using one highly-effective form of birth control (the participant should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study and continue to 7 months after the last dose).

A more detailed description of the required lifestyle restrictions relating to reproduction is provided in Section 5.3.1.

Genomics Initiative Research Study (Optional):

For inclusion in the optional Genomics Initiative component of the study, participants must fulfil the following additional criteria:

1 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of saliva samples for optional genetic research that supports Genomics Initiative. If a participant declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the participant. The participant will not be excluded from other aspects of the study described in this protocol, so long as they consented to the main study.

Tumour Biopsy At Disease Progression (Optional):

For inclusion in the optional tumour biopsy component of the study, participants must fulfil the following additional criteria:

1 Provision of signed, written, and dated informed consent for tumour biopsy at disease progression. If a participant declines to participate in the tumour biopsy component of the study, there will be no penalty or loss of benefit to the participant. The participant will not be excluded from other aspects of the study described in this protocol, so long as they consented to the main study.

2 Having an accessible tumour/lymphadenopathy and a stable clinical condition that will allow the participant to tolerate the procedure, if deemed safe and feasible by the Investigator.

Refer to the individual modules for additional module-specific inclusion criteria.

5.2 Exclusion Criteria – Core

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Participants with non-secretory myeloma.

2 With the exception of alopecia, any unresolved non-haematological toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment.

3 Presence of, or history of, central nervous system (CNS) lymphoma, leptomeningeal disease, or spinal cord compression.

4 History of prior non-haematological malignancy except for the following:

(a) Malignancy treated with curative intent and with no evidence of active disease present for more than one year before Screening and felt to be at low risk for recurrence by treating physician.

(b) Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer.

(c) Adequately treated carcinoma in situ without current evidence of disease.

5 As judged by the Investigator, any evidence of severe or uncontrolled systemic disease (eg, severe hepatic impairment, interstitial lung disease [bilateral, diffuse, parenchymal lung disease]), or current unstable or uncompensated respiratory or cardiac conditions, or uncontrolled hypertension, history of, or active, bleeding diatheses (eg, haemophilia or von Willebrand disease) or uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment), or IV anti-infective treatment within two weeks before first dose of study drug.

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

7 Serologic status reflecting active hepatitis B or C infection:

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

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

8 Any of the following cardiac criteria:

(a) Resting QT interval corrected using Fridericia's formula (QTcF) $\geq$ 470 msec obtained from a single ECG.

(b) Any clinically important abnormalities in rhythm (except for participants with a pacemaker in place), conduction or morphology of resting ECG (eg, complete left bundle branch block, third degree heart block).

(c) Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age. Concomitant medications known to prolong QTc should be used with caution and cannot be used starting with the first dose of study drug and through the DLT-assessment period (Part A) or during the scheduled ECG assessments.

9 History of severe allergic or anaphylactic reactions to BH3 mimetics or history of hypersensitivity to active or inactive excipients of study treatment.

10 Documented confirmation and ongoing treatment of adrenal gland insufficiency or pancreatitis.

11 Undergone any of the following procedures or experienced any of the following conditions within 6 months prior to first dose:

(a) coronary artery bypass graft

(b) angioplasty

(c) vascular stent:

(i) A participant who has had a cardiac stent or arterial stent implanted within 6 months prior to first dose, is not eligible for the study.

(ii) A participant who has had a venous stent implanted within 6 months prior to first dose, is eligible for the study.

(d) myocardial infarction

(e) angina pectoris

(f) congestive heart failure (New York Heart Association Class ≥ 2)

(g) ventricular arrhythmias requiring continuous therapy

(h) atrial fibrillation, which is judged as uncontrolled by the treating physician

(i) haemorrhagic or thrombotic stroke, including transient ischaemic attacks or any other CNS bleeding

Prior/Concomitant Therapy

12 Treatment with any of the following:

(a) Received cytotoxic chemotherapy within 21 days (or 42 days for nitrosoureas or mitomycin C).

(b) Received radiotherapy within 14 days.

(c) Received major surgery (as defined by the Investigator), or immunotherapy (specifically immune checkpoint inhibitors) within 28 days.

(d) Received adoptive cellular therapy such as autologous or donor natural killer (NK) cell or T lymphocyte infusions [eg, CAR-T cells]) within 60 days.

(e) Received an investigational drug within 14 days of the first scheduled dose or not recovered from associated toxicities.

(f) Participants who have previously received an autologous stem cell transplantation (SCT) are excluded if less than 90 days have elapsed from the time of transplant or the participant has not recovered from transplant-associated toxicities prior to the first scheduled dose.

(g) Participants with a history of allogeneic SCT are excluded, UNLESS the following eligibility criteria are met: transplant was > 180 days prior to the first scheduled dose AND participant must not have taken immunosuppressive medications associated with the transplant for at least 1 month prior to first scheduled dose.

13 Requires ongoing immunosuppressive therapy, including systemic (eg, intravenous or oral) corticosteroids for treatment of lymphoid cancer or other conditions. Note: Participants may use topical or inhaled corticosteroids or low-dose steroids (≤ 10 mg of prednisone or equivalent per day) as therapy for comorbid conditions. Short courses of steroids before study entry are allowed. During study participation, participants may also receive systemic corticosteroids as needed for treatment-emergent comorbid conditions.

14 Receipt of live, attenuated vaccine within 28 days before the first dose of study treatment(s).

Other Exclusions

15 Judgement by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

In addition, the following is considered a criterion for exclusion from the optional genetic research:

- Previous allogeneic bone marrow transplant

Refer to the individual modules for additional module-specific exclusion criteria.

5.3 Lifestyle Considerations

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

5.3.1 Reproduction

The following restrictions apply while the participant is receiving AZD4573 and for the specified times before and after:

- Female participants must be one year post-menopausal, surgically sterile, or using one highly-effective form of birth control (a highly-effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly). Women of childbearing potential should use highly-effective methods of contraception (see Table 3). They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study until 7 months after discontinuing AZD4573.
- Female participants must not donate, or retrieve for their own use, ova from the time of start of dosing and throughout the study treatment period, and for at least 7 months after the final study drug administration.

Note: True abstinence can only be used as the sole method of contraception if it is consistently employed as the participant's preferred and usual lifestyle, and if considered acceptable by local regulatory agencies and IRB/Independent Ethics Committees (IEC). Periodic abstinence (eg, calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Male participants should be asked to avoid unprotected sex (ie, always use a condom) with women of childbearing potential during the study and for a washout period of 4 months after discontinuing AZD4573. Female partners of male participants should use highly-effective methods of contraception for the duration of the study and for a washout period of 4 months after their partner discontinues AZD4573. Male participants should refrain from donating sperm from the start of dosing until 4 months after discontinuing AZD4573. If male participants wish to father children, they should be advised to arrange for freezing of sperm samples before the start of receiving AZD4573.

Table 3 Highly-Effective Methods of Contraception

Barrier/Intrauterine methods	• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]
Hormonal methods	• Implants[b]: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal Devices[b]: Ethinyl oestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Injection[b]: Medroxyprogesterone injection: eg, Depo-Provera® • Combined Pill: Normal and low-dose combined oral contraceptive pill • Patch[b] : Norelgestromin/ethinyl oestradiol-releasing transdermal system (eg, Ortho Evra®) • Minipill[b]: Progesterone based oral contraceptive pill using desogestrel. Cerazette® is currently the only highly-effective progesterone-based pill

[a] This is also considered a hormonal method
[b] Not approved for use in Japan

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from Regulatory Authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned the same participant enrolment number as for the initial screening. The Investigator should confirm this with the designated study physician.

6 STUDY INTERVENTION - CORE

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Please refer to the following modules outlining the specific treatment details:

- Module 1: AZD4573 + acalabrutinib in participants with r/r DLBCL or r/r MZL.

- Module 2: AZD4573 monotherapy followed by AZD4573 + acalabrutinib in participants with r/r MCL.

Additional modules and combinations of AZD4573 with other anti-cancer agents may be added in the future by amendment.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

AZD4573 will be administered as an absolute (flat) dose, 2-hour (± 15 minutes) IV infusion once weekly, at least 5 days apart, in combination with other anti-cancer agents (initial frequencies, schedules, and sequencing of AZD4573 dosing with respect to the combination agent(s) will be defined in their respective module; alternate frequencies, schedules, and sequences may be instigated in response to emerging safety, tolerability, or PK data via a protocol amendment).

For all participants, results of safety laboratory testing (haematology and clinical chemistry at a minimum) must be available prior to dosing and must be reviewed by the Investigator prior to each administration of AZD4573.

Liver chemistry tests: **For any participant on study who experiences elevated ALT /AST ≥ 3 × ULN and/or elevated total bilirubin ≥ 2 × ULN**: repeated liver chemistry tests (INR, fibrinogen, D-dimer [where available at institution], alkaline phosphatase (ALP), ALT, AST, glutamic dehydrogenase (GLDH), creatinine phosphokinase (CPK), total bilirubin, direct bilirubin, indirect bilirubin) are required at 48 hours (-2/+12 hours) and 96 hours (- 2/+12 hours) after the start of the infusion and until resolution of the event. However, in case the event is not resolved within 96 hours the medical monitor should be contacted. If GLDH cannot be performed locally, LDH will be analysed locally and a serum sample must be collected for central retrospective GLDH analysis. Refer to the Laboratory Manual for details.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential Hy's Law (PHL) criteria at any point during the study. The Investigator participates, together with the Sponsor, in review and assessment of these cases. Hy's Law (HL) criteria are met if there is no alternative explanation for the elevations in transaminases and total bilirubin levels.

If an unscheduled ECG is done at any time: troponin and an electrolyte panel* must be done to coincide with the ECG testing.

* can include: sodium, calcium, potassium, chloride, phosphate, magnesium.

If a participant is assessed as meeting PHL criteria, please refer to Appendix E.

In case of any unacceptable deterioration in laboratory values, not fulfilling eligibility criteria, and deemed as clinically significant by the Investigator, the Medical Monitor must be contacted to discuss whether AZD4573 dosing can be continued.

AZD4573 will be supplied by the Sponsor. CCI [redacted]

Please refer to the individual study modules for the method of supply of combination agents.

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines by AstraZeneca Research & Development supply chain. The labels will fulfil Good Manufacturing Practice Annex 13 requirements for labelling. Label text will be translated into local language.

All IPs should be kept in a secure place under appropriate storage conditions. The appropriate storage conditions for AZD4573 and combination agents will be defined on the product label.

6.2 Starting Dose, Dose-Escalation Scheme, and Stopping Criteria

Refer to each protocol module for further details of the dose-escalation-decision rules and information for the combination agents used.

A study-specific SRC, in accordance with its charter, will be responsible for making recommendations for dose escalation or dose de-escalation decisions, including decisions on opening cohorts for backfill, as well as making recommendations regarding further conduct of the study. The SRC will review available clinical and laboratory safety data and other relevant data prior to making recommendations.

6.3 Definition of Dose-limiting Toxicity (DLT)

DLTs will be defined in individual study modules.

6.4 Definition of Maximum Tolerated Dose (MTD)

MTDs will be defined in individual study modules.

6.5 Definition of Recommended Phase II Dose (RP2D)

The RP2D will be defined in individual study modules.

6.6 Definition of Evaluable Participant

Evaluable participants will be defined in individual study modules.

6.7 Duration of Therapy

Duration of therapy will be defined in individual study modules.

6.8 Preparation/Handling/Storage/Accountability of Interventions

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

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

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

CCI [redacted]

AZD4573 should only be used as directed in this protocol and as detailed in a separate Handling Instructions document for AZD4573. Details of treatment with AZD4573 for each participant will be recorded in the eCRF. CCI [redacted]

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

All study supplies and associated documentation will be regularly reviewed and verified by the site monitor before destruction.

6.9 Measures to Minimise Bias: Randomisation and Blinding

This is a non-randomised study. Each potential participant approved for screening is assigned a unique participant enrolment number. If a participant withdraws from the study, then the enrolment number cannot be reused.

6.10 Study Intervention Compliance

Refer to individual study modules for study intervention compliance.

6.11 Prior/Concomitant Therapy

Information on any treatment received in the 30 days before starting IP and all concomitant treatments given during the study, with reasons for the treatment, will be recorded in the eCRF. If medically feasible, participants taking regular medication should be maintained on it throughout the study period.

Any prophylactic treatment given as part of the study is to be recorded in the eCRF as concomitant therapy.

AZD4573 and concomitant treatments are described below, refer to individual study modules for other study interventions.

AZD4573 and concomitant treatments

Given the proposed clinical dosing regimen of AZD4573, a short IV infusion over 2 hours (once weekly), and the observed short half-life of approximately 4 to 7 hours, the risk of clinically meaningful drug interactions with AZD4573 is considered to be low.

In vitro studies suggest AZD4573 could reversibly inhibit cytochrome P450 (CYP)3A4/5, CYP2C8, CYP2C9, CYP2C19, organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2 and multi-antimicrobial extrusion protein (MATE). However, clinical studies have not yet been performed to assess drug-drug interaction. Based on the static model recommended (FDA 2017), exposure increase of CYP3A-sensitive substrates caused by AZD4573 will be 1.06, making it a weak inhibitor.

AZD4573 is not a strong inducer of CYP1A2, CYP2B6, or CYP3A, based on in vitro studies.

If potent CYP3A4 inhibitors are administered, it is recommended to avoid administering them on the same day as AZD4573 administration where possible. Alternatively, such inhibitors could be administered 8 to 12 hours after the completion of the AZD4573 infusion, if deemed clinically warranted in the opinion of the Investigator.

It is recommended that treatment with strong CYP3A4 inducers is avoided, unless it is deemed clinically warranted in the opinion of the Investigator.

Concomitant drugs that have the potential to prolong QTc, should not be used around the time of the scheduled ECG assessments during this study.

Concomitant use of paracetamol is permitted but is limited to a maximum dose of 4 grams per day. Other anti-cancer agents, investigational agents (other than co-administered agents described in the study module), or radiotherapy should not be given while the participant is taking AZD4573, although radiation for palliation at focal sites is permitted after discussion with the Medical Monitor.

After the start of study intervention, blood and platelet transfusions are allowed as clinically indicated at any time during the study and can be given as per local institutional guidelines.

Supportive care (eg, recombinant growth factor support), and other medications that are considered necessary for the participant's wellbeing (eg, bisphosphonates), may be given at the discretion of the Investigator and in accordance with local institutional guidelines.

At study entry, participants may be using topical or inhaled corticosteroids or low-dose steroids (≤ 10 mg of prednisone or equivalent per day) as therapy for comorbid conditions, but use of corticosteroids as therapy for lymphoid cancer is not permitted. Doses of systemic corticosteroid > 10 mg/day may be used during the study if clinically indicated (eg, for treatment of an AE/SAE), but the dose must be tapered back down to no greater than 10 mg/day upon resolution of the event, to avoid chronic use.

AstraZeneca recommends administering non-live inactivated vaccines 72 hours prior to administration of the first dose of any IP to avoid biases in the interpretation of safety data due to the potential overlap of vaccine-related AEs with IP AEs.

6.12 Dose Modification

If, in the opinion of the Investigator, a participant experiences a clinically significant and/or unacceptable adverse reaction, including a DLT not attributable to the disease or disease-related processes under investigation, but is considered to be possibly related to AZD4573 by the Investigator, then the dose may be temporarily or permanently halted or reduced.

Supportive therapy will be administered as required. Relevant reporting and discussion with the Medical Monitor will take place before resumption of dosing.

Events meeting the definition of a DLT as defined in the specific study modules must be

reported accordingly. Refer to specific study modules for dose modifications.

6.12.1 Retreatment Criteria

Retreatment is defined as the first dose of study drug after a period of intentional pause in study drug treatment (other than missed doses, eg, study treatment put on hold until resolution of COVID-19). Refer to specific study modules for retreatment criteria.

6.13 Intervention After the End of the Study

After the data cut-off for the primary analysis, the clinical study database will be closed to the entry of new data. However, patients still receiving AZD4573 at that time will be able to continue receiving study treatment (in accordance with guidance in this protocol and the IB) if, in the opinion of the Investigator, they are still deriving clinical benefit.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL - CORE

7.1 Discontinuation of Study Intervention

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Participants must be discontinued from study intervention in the following situations:

- Participant decision. The participant is at any time free to withdraw his/her participation in the study, without prejudice
  - Withdrawal of consent from the study
  - Withdrawal of consent from further treatment with IP
- Investigator decision
- Any AE that meets criteria for discontinuation of IP as defined in Section 8.2
- Initiation of alternative anti-cancer therapy including another investigational agent
- Investigator determination that the participant is no longer benefiting from the treatment regimen
- Severe noncompliance to this protocol as judged by the Investigator and/or AstraZeneca
- Confirmed disease progression
- Participant is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing treatment with IP might constitute a safety risk (Section 7.3)
- A female participant becomes pregnant

Participants that are withdrawn from the study but are evaluable per the definition in each module will not be replaced. Any participant that is withdrawn and is not evaluable may be replaced to ensure a minimum number of evaluable participants.

Participants may withdraw from any aspect of the voluntary exploratory research at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study. Procedures for withdrawal from the exploratory research are outlined in Appendix C 2. The medical care that a participant may receive after the study has ended may involve a different drug or treatment, which the hospital, together with the Investigator considers to be the most suitable alternative. The Investigator will be responsible for making arrangements for the continuation of a participant's medical care after participation in this study has ended.

7.1.1 Temporary Discontinuation

Applicable criteria and procedures for restarting study intervention will be defined in individual study modules.

7.1.2 Rechallenge

Applicable rechallenge procedures will be defined in individual study modules.

7.2 Participant Withdrawal from the Study

All participants will be followed for survival until death, loss to follow-up, AstraZeneca closes the study, or withdrawal of consent, whichever occurs first.

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons.
- A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, the 30-day Safety Follow-Up (SFU) visit should be conducted, as shown in the SoA. See the SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

In addition, participants may be withdrawn from the study in the event that the Sponsor terminates this study (see Appendix A 9).

7.3 Procedures for Handling Participants Incorrectly Initiated on AZD4573 or Combination Therapy

Any participants determined to have met one or more of the exclusion criteria for study participation at study entry and continuing treatment with IP might constitute a safety risk.

Where participants that do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment with AZD4573 or combination therapy, or where participants subsequently fail to meet the study criteria after initiation of treatment, the Investigator should inform the Medical Monitor immediately. The Medical Monitor is to ensure all such contacts are appropriately documented.

7.4 Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A 9.

8 STUDY ASSESSMENTS AND PROCEDURES - CORE

- Study procedures and their timing for each module are summarised in the SoA for that module. Protocol waivers or exemptions are not allowed.

- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the informed consent form (ICF) may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Refer to the specific study modules for the maximum amount of blood collected from each participant over the duration of the study.

8.1 Safety Assessments

Refer to the specific study modules for the safety assessments in this study.

8.2 Adverse Events and Serious Adverse Events

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

The definitions of an AE or SAE can be found in Appendix B 1 and Appendix B 2.

An AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.2.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs will be collected and recorded from the time of signing of the ICF throughout the treatment period and including the follow-up period, 30 days after the last dose of study intervention.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product that occurs after the end of the SFU period in a participant

treated by him or her, the Investigator shall, without undue delay, report the SAE to the Sponsor.

8.2.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

The following variables will be collected for each AE:

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

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

- Date AE met criteria for SAE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication
- Detailed information on the event (symptoms and signs, work-up done)

8.2.3 Causality Collection

The Investigator should assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IP?'

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

A guide to the interpretation of the causality question is found in Appendix B 3 to the CSP.

8.2.4 Adverse Events Based on Signs and Symptoms

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

8.2.5 Adverse Events Based on Examinations and Tests

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

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

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

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE.

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

In case TLS is observed at any time during the study, this should be reported as an AE and on the AE page of the eCRF (in addition to the completion of applicable TLS monitoring forms), the TLS should be graded according to CTCAE on the AE page.

8.2.6 Potential Hy's Law Cases

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN **must be reported as SAEs due to medical significance**. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of HL. Please also refer to specific dose modification guidance contained in each module for use in events of PHL. Discussions regarding study drug discontinuation (eg, with the Medical Monitor) due to increased liver transaminases and/or bilirubin increases should be documented.

8.2.7 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis, to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study. Death clearly resulting from disease progression should not be reported as an SAE.

8.2.8 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria. New cancers are those that are not the primary reason for the administration of the study treatments and have been identified after the participant's inclusion in this study. They do not include metastases of the original cancer.

8.2.9 Handling of Deaths

All deaths that occur during the treatment period including SFU period should be reported as follows:

- Death that is unequivocally due to disease progression should be communicated to the study monitor/medical monitor as soon as possible and be documented in the relevant eCRF module, but it should not be reported as an SAE during the study.

- Where death is not clearly due to the progression of the disease under study, the AE causing the death should be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death, together with any contributory causes. Autopsy report should be requested if available.
- Deaths with an unknown cause should always be reported as an SAE, but every effort should be made to establish a cause of death. A post-mortem may be helpful for the cause-of-death assessment and, if performed, a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes.
- Deaths that occur after the treatment period during the survival follow-up period should be reported on the survival log on the eCRF.

8.2.10 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

Participants continuing study treatment after the end of data collection for the primary analysis will be followed for SAEs with paper reporting instead of eCRF reporting.

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

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

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

Once the investigators or other site personnel indicate an AE is serious in the eCRF system, an automated email alert will be sent to the designated AstraZeneca representative.

If the electronic data capture (EDC) system is not available, then the Investigator or other study-site staff will report a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study-site staff how to proceed.

CCI [redacted]

Participants 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). If a participant has no signs of laboratory TLS at the 6-hour TLS monitoring assessment, the participant may leave the clinic after the collection of other laboratory samples, as per the SoA, at 7 hours after the start of the infusion and managed as an outpatient, at the discretion of the Investigator. These participants must return to the clinic the next morning to complete the 24-hour TLS monitoring period as per the SoA (Cycle 1 Weeks 1-3). Participants with TLS at the 6-hour TLS monitoring assessment must be admitted for in-patient TLS monitoring for a minimum of 24 hours after the start of the infusion and monitored every 4 to 6 hours during this time (or more frequently if clinically indicated).

Sites retain the option to hospitalise participants based on clinical judgement, despite normal TLS laboratory results 6 hours after the start of the infusion. Admitting the participant for subsequent dose administrations will be done at Investigator discretion.

Any hospitalisation due to occurrence of an AE must be reported as an SAE, per definition. However, if hospitalisation is purely for the purposes of extended observation then this does not qualify as an SAE and does not need to be reported.

8.2.11 Adverse Events of Special Interest for AZD4573

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

The following are considered to be AESIs for AZD4573:

- Tumour lysis syndrome
- Hepatotoxicity (including PHL, drug-induced liver injury (DILI), and bilirubin increase with transaminase (ALT or AST or both ALT and AST) increase
- Neutropenia (including Febrile neutropenia, Neutropenic sepsis, and Neutrophil count decrease
- Thrombocytopenia, including Platelet count decrease
- Myocardial ischaemia
- Pyrexia

8.2.12 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca, except when the pregnancy is discovered before the participant has received AZD4573.

If a pregnancy is reported, the Investigator should inform AstraZeneca within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.2.12.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, IP should be discontinued immediately.

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

If any pregnancy occurs in a female participant during exposure to IP or in the 7 months after discontinuing the IP, then the Investigator or other site personnel will inform the appropriate AstraZeneca representatives within one day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within one

or 5 calendar days for SAEs (see Section 8.2.10) and within 30 days for all other pregnancies. The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

8.2.12.2 Paternal Exposure

Pregnancy of a participant's partner is not considered to be an AE. However, any conception occurring from the date of dosing until 4 months after discontinuation of dosing should be reported to AstraZeneca and followed up for its outcome.

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

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

8.2.13 Medication Error

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

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is completed within one (Initial Fatal/Life-Threatening or Follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.2.10) and within 30 days for all other medication errors.

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

8.3 Overdose

For this study, any dose of study intervention greater than the dose that was intended to be given will be considered an overdose.

All overdoses should be recorded as follows:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

- An overdose without associated symptoms is only reported on the Overdose eCRF module.

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

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within one or 5 calendar days for overdoses associated with an SAE (see Section 8.2.10) and within 30 days for all other overdoses.

For AZD4573, no data on overdosing are available. There is no known antidote for AZD4573. Investigators should be advised that any participant who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care under local institutional guidelines and followed up expectantly.

Refer to individual study modules for overdose information on the other anti-cancer agents being used in combination with AZD4573.

8.4 Efficacy Assessments

Refer to the individual study modules for the efficacy assessments in this study.

8.5 Human Biological Samples

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

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

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

Details of sample collection, processing, shipping and storage of samples for exploratory research will be described in the Laboratory Manual. Each sample for exploratory research will be identified with the study number and participant enrolment number.

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples may be stored for a maximum of 15 years or as per local regulations from the date of the last participant's last visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organizations working with the DNA.

8.5.1 Pharmacokinetics

Refer to the individual study modules for the assessments of PK in this study.

8.5.2 Pharmacodynamics

Refer to the individual study modules for the assessments of pharmacodynamics in this study.

8.6 CCI [redacted]

Refer to the individual study modules for the assessments CCI [redacted] in this study.

8.7 Optional Genomics Initiative Sample

Refer to the individual study modules for information on the optional collection of samples for genetic research in this study.

8.8 Health Economics OR Medical Resource Utilisation and Health Economics

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

9 STATISTICAL CONSIDERATIONS – CORE

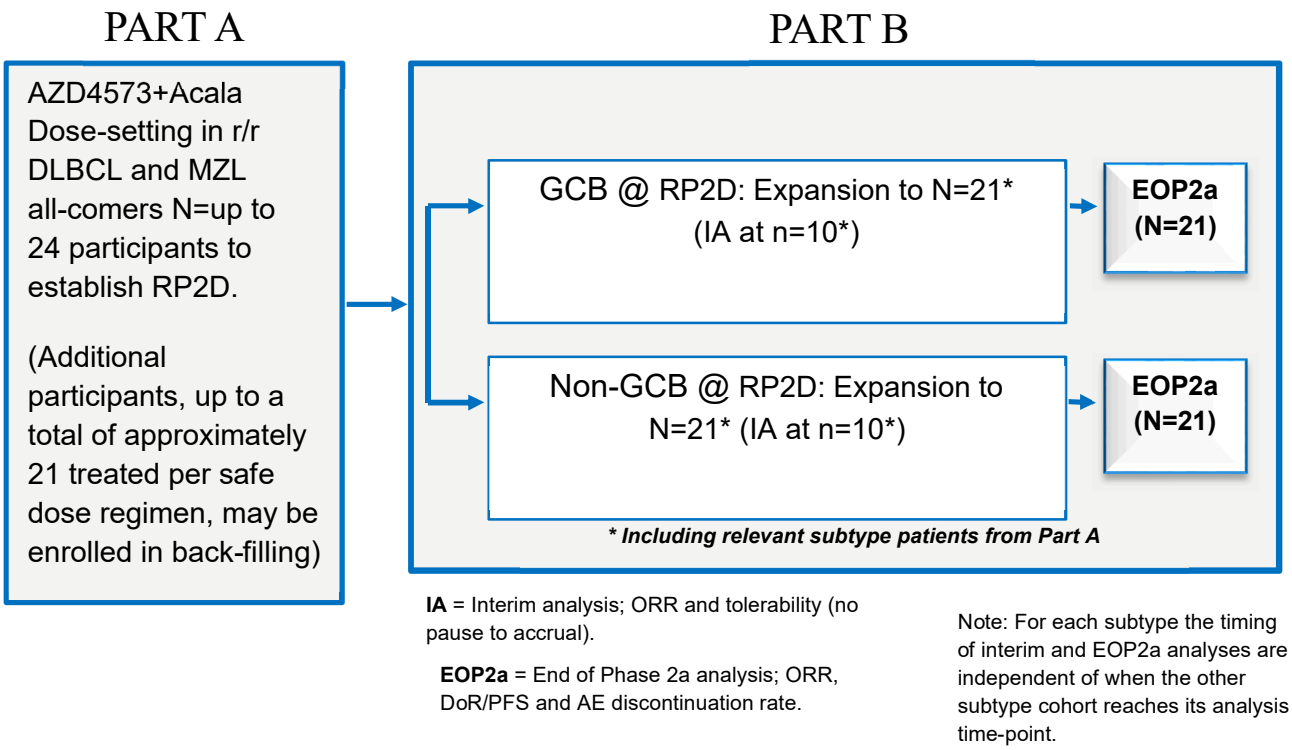
Refer to the individual study modules for the statistical considerations in this study.

MODULE 1: AZD4573 PLUS ACALABRUTINIB IN PARTICIPANTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) OR RELAPSED OR REFRACTORY MARGINAL ZONE LYMPHOMA (MZL)

10 PROTOCOL SUMMARY – MODULE 1

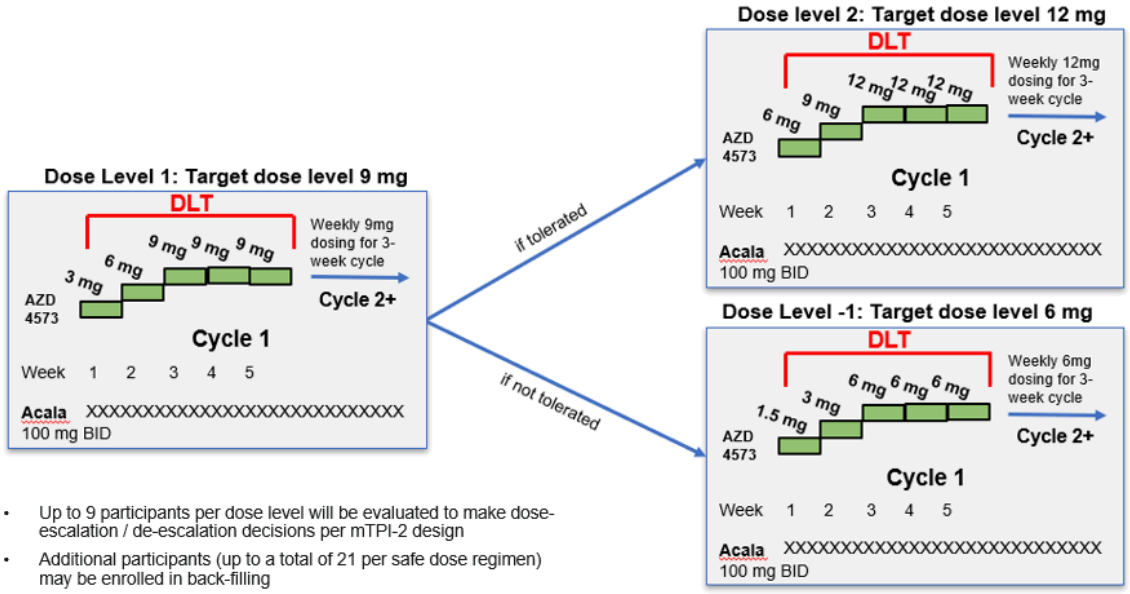
10.1 Schema

Figure 4 **Module 1 Overall Study Design for AZD4573 in Combination with Acalabrutinib in Participants with Relapsed or Refractory DLBCL or Relapsed or Refractory MZL**



Note: Part A includes 'All-comer' participants with relapsed or refractory large B-cell lymphoma including subtypes such as DLBCL NOS, HGBCL, PMBCL, or large B-cell lymphoma transformed from indolent B-cell lymphomas (including Richter Syndrome, transformed Follicular Lymphoma, transformed marginal zone lymphoma) or participants with r/r MZL. Part B only includes participants with de novo DLBCL (GCB or non-GCB).
Abbreviations: AE = adverse event; DLBCL = diffuse large B-cell lymphoma; DoR = duration of response; EOP2a = end of Phase IIA; GCB = germinal centre B-cell; HGBCL = high-grade B-cell lymphoma; IA = interim analysis; MZL = marginal zone lymphoma; NOS = not otherwise specified; ORR = objective response rate; PFS = progression-free survival; PMBCL = primary mediastinal B-cell lymphoma; r/r = relapsed/refractory; RP2D = recommended Phase II dose.

Figure 5 Module 1 Part A (Dose Setting) Study Design



Dosing will be staggered by at least one week between the first and the second participant dosed in each new dose level cohort. Subsequent participants dosed will be staggered by a minimum of 3 days until a decision is made regarding dose escalation or de-escalation.
After completion of the 5-week DLT-assessment period, treatment with AZD4573 and acalabrutinib may be continued until disease progression, an unacceptable drug-related toxicity occurs as defined in the protocol, or the participant withdraws or is withdrawn from the study for other reasons.
Abbreviations: BID = twice daily; DLT = dose-limiting toxicity; mTPI = modified toxicity probability interval.

10.2 Schedules of Activities – Module 1

Table 4 Schedule of Activities: Module 1 (AZD4573 with Acalabrutinib) Part A – Dose Setting Cohorts

Assessment	Screen[a]	Cycle 1, Weeks 1-5 (includes intra-patient Dose ramp up)	Cycles 2-8 (Cycle=21 Days)			Cycles 9+ (Cycle = 21 days)[ll]	Disease Assessment[b]/ End of Treatment[mm]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(±2 Days)	(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Informed consent[d]	X									Section 17.1.1
Inclusion/exclusion	X									Section 17.1.1
Medical history and demographics	X									Section 17.1.1
Physical examination[f]	X	X	X	X	X	X		X		Section 17.1.2
ECOG performance status	X	X	X	X	X	X		X		Section 17.1.4
Archival tumour sample or new biopsy	X									Section 17.10.1 17.1.10.2

Assessment	Screen[a]	Cycle 1, Weeks 1-5 (includes intra-patient Dose ramp up)	Cycles 2-8 (Cycle=21 Days)			Cycles 9+ (Cycle = 21 days)[ll]	Disease Assessment[b]/ End of Treatment[mm]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(±2 Days)	(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Vital signs[e]	X	X	X	X	X	X (each infusion)		X		Section 17.1.3
Weight[f]	X	X	X			X		X		Section 17.1.3
B symptoms	X	X	X	X	X	X		X		Section 17.1.5
12-lead ECG[g]	X	X	X			X		X		Section 17.1.8
CMV immunoglobulin M [IgM] and PCR[h]	X									Section 14.2, 17.1.6
Cardiac troponin[i]	X	X	X			X		X		Section 17.1.6
T4, Cortisol, ACTH and TSH[j]	X		X (Cycle 2 only)					X		Section 17.1.6
ECHO/MUGA[k]	X	As clinically indicated[k]						X[k]		Section 17.1.7

Assessment	Screen[a]	Cycle 1, Weeks 1-5 (includes intra-patient Dose ramp up)	Cycles 2-8 (Cycle=21 Days)			Cycles 9+ (Cycle = 21 days)[ll]	Disease Assessment[b]/ End of Treatment[mm]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(±2 Days)	(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Haematology[l]	X	X	X	X	X	X[l] (each infusion)		X		Section 17.1.6
Coagulation[m]	X	X	X	X	X	X[m]		X		Section 17.1.6
Clinical chemistry[n]	X	X	X	X	X	X[n] (each infusion)		X		Section 17.1.6
TLS monitoring[o]		Weeks 1-3								Section 17.1.10.10
Urinalysis[p]	X	X	X	X	X	X		X		Section 17.1.6
Pregnancy testing (women of childbearing potential)[q]	X (Serum)	Week 1 (predose)	Once every 21 days (±7 days)					X		Section 17.1.6
Lipase/amylase[r]	X	X	X	X	X	X		X		Section 17.1.6

Assessment	Screen[a]	Cycle 1, Weeks 1-5 (includes intra-patient Dose ramp up)	Cycles 2-8 (Cycle=21 Days)			Cycles 9+ (Cycle = 21 days)[ll]	Disease Assessment[b]/ End of Treatment[mm]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(±2 Days)	(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Hepatitis serology[s]	X		See footnote for schedule							Section 17.1.6 and Section 17.1.10.4
CD4, CD8, CD19, CD16/NK cell count[t]	X		See footnote for schedule					X		Section 17.1.7
Serum immunoglobulins (IgA, IgM, IgG)[t]	X		See footnote for schedule					X		Section 17.1.7
Concomitant medication	X	X	X	X	X	X (each infusion)	X	X	X	Section 15.11
Adverse event evaluation	X	X	X	X	X	X (each infusion)	X	X	X	Section 8.2
AZD4573/ acalabrutinib plasma PK[u]		Weeks 1-3	Cycle 2							Section 17.6

Assessment	Screen[a]	Cycle 1, Weeks 1-5 (includes intra-patient Dose ramp up)	Cycles 2-8 (Cycle=21 Days)			Cycles 9+ (Cycle = 21 days)[ll]	Disease Assessment[b]/ End of Treatment[mm]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(±2 Days)	(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Pharmacodynamic samples (blood) for AZD4573[v]		Weeks 1-3[v]								Section 17.7
Pharmacodynamic samples (blood) for acalabrutinib[w]		Week 1 and Week 4[w]								Section 17.7
CCI [redacted]	X	Weeks 1-3	CCI [redacted]							Section 17.8
Whole blood for exploratory CCI [redacted]	X	Weeks 1, 3, and 5	Cycles 2, 3, 5, 6, and 7		Cycle 2		X	(X)		Section 17.9.1
Whole Blood for CCI [redacted]	X	Weeks 1, 3 and 5	Cycles 2, 3, 5, 6, and 7		Cycle 2		X	(X)		Section 17.9.2
Whole Blood Samples for CCI [redacted]	X	Weeks 1 and 3	Cycles 2, 3, 5, and 7		Cycle 2		X	(X)		Section 17.9.3

Assessment	Screen[a]	Cycle 1, Weeks 1-5 (includes intra-patient Dose ramp up)	Cycles 2-8 (Cycle=21 Days)			Cycles 9+ (Cycle = 21 days)[ll]	Disease Assessment[b]/ End of Treatment[mm]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(±2 Days)	(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Whole blood samples for [redacted]	X	Weeks 1 and 3	Cycle 2		Cycle 2		X	(X)		Section 17.9.4
Exploratory blood [redacted]	X	Weeks 1-3	Cycles 2, 3, 5, and 7				X	(X)		Section 17.9.6
[redacted] sample for [redacted] isolation[dd]	(X)	Week 1 (predose)								Section 17.10.4.1
Genomics Initiative saliva sample (optional)[ee]	(X)	Week 1 (predose) X	(X)	(X)	(X)	(X)	(X)	(X)		Section 17.11
Tumour biopsy sample (optional)[ff]							At disease progression	(X)[ff]		Section 17.10.5.1

Assessment	Screen[a]	Cycle 1, Weeks 1-5 (includes intra-patient Dose ramp up)	Cycles 2-8 (Cycle=21 Days)			Cycles 9+ (Cycle = 21 days)[ll]	Disease Assessment[b]/ End of Treatment[mm]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(±2 Days)	(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Bone marrow biopsy & aspirate[gg]	X						As clinically indicated and to confirm CR			Section 17.4.3 and Section 17.10.3
Disease assessment[b] and radiologic scans[hh]	X	See Table 19 for schedule						X		Section 17.4.2
Acalabrutinib oral, BID[ii]		Twice daily (from Cycle 1, Week 1 to end of treatment)								Section 15.1
AZD4573 intravenous[ij]		Once weekly (from Cycle 1, Week 1 to end of treatment)[nn]								Section 15.1
Acalabrutinib drug accountability[kk]		X	X	X	X	X				Section 15.8
Disease progression follow-up (SoC)									X	Section 17.1.9.2
Survival Follow-up									X	Section 17.1.9.3

[a] Screening tests should be performed within 30 days before the first administration of study drug, unless otherwise indicated.

[b] Disease assessments will be done by the Investigator using the Lugano Response Criteria for Non-Hodgkin's Lymphoma (Cheson et al 2014). Additional disease assessments may be performed as clinically indicated.

[c] The SFU visit will be performed 30 days (±7 days) after the last dose of all study drug. Tumour assessments will be repeated at this visit if they have not been performed within 9 weeks if the participant discontinued before or during Week 26, or 12 weeks if the participant discontinued after Week 26.

[d] Informed consent must be obtained ≤ 30 days before the first dose of study drug and must be obtained before any protocol-defined screening procedures are done.

[e] Vital signs (blood pressure, pulse rate, temperature) will be assessed after the participant has rested for at least 10 mins. Blood pressure and pulse rate will be measured at Screening, and on Day 1 of Cycle 1, Weeks 1-3 at the following timepoints: predose (within 2 h prior to infusion), 1 h after the start of the infusion (± 10 mins), at end of infusion (up to 10 mins post dose) and then 4 h (± 30 mins) and 6 h (± 30 mins) after start of infusion, from Cycle 1 Week 4 onwards, at predose (up to 30 mins prior to infusion), at the end of infusion (up to 30 mins post dose), and at the 30-day SFU. Temperature to be taken pre-infusion (up to 2 h prior to all infusions).

[f] As the study is intended to recruit adults, height should only be measured at Screening. Weight to be measured at Screening, prior to infusions on Day 1 of each cycle, and at the 30-day SFU visit.

[g] Participants should be in semi-supine position and resting for ≥ 10 mins before the ECGs. Single ECGs for local and central analysis are required at Screening and at the following timepoints: for Cycle 1, Weeks 1-5 and Cycle 2 Day 1 predose (at the day of infusion prior to infusion) and within 30 mins of the end of infusion; for Cycles 3+ on Day 1 within 30 mins after the end of infusion, and at the 30-day SFU visit.

[h] All subjects will have CMV testing at Screening including serology testing for CMV immunoglobulin (Ig)G and CMV IgM and CMV DNA PCR testing

[i] Cardiac troponin measurements are required at the following timepoints: Screening, Cycle 1, Weeks 1-5, predose (within 72 hours prior to infusion) and at 24 h after the start of the infusion, and Cycles 2+ on Day 1 of each cycle, predose (within 72 hours prior to infusion), and at the 30-day SFU visit. Note: either a troponin I or troponin T assay can be used per SoC at the respective hospital. If the hospital has both a SoC troponin I and troponin T assay available, the investigator shall use only one consistently for the duration of the study.

[j] T4, cortisol, ACTH, and TSH to be taken at Screening, predose (within 72 hours prior to infusion) on Cycle 2, Day 1, and at the 30-day SFU.

[k] ECHO should be done at Screening and within 14 days after an abnormal ECG finding (eg, T-wave inversion/flattening) or as soon as possible when clinically indicated. If an ECHO cannot be taken, a MUGA scan to assess LVEF will be done. In case of any T-wave abnormality, the ECHO (or MUGA) should be repeated at the 30-day follow-up visit to address the question of recovery, during the off-treatment period.

[l] Haematology testing should be measured at Screening, Cycles 1, 2, and 3 predose (within 72 h prior to infusion) and 24 h after the start of the infusion. From Cycle 4 onwards, haematology testing should be predose (within 72 h prior to infusion) and (if clinically indicated) 24 h after the start of the infusion. A sample will also be drawn at the 30-day SFU. The Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF. Haematology tests do not need to be repeated before first dose if the first-dose visit is within 3 days of the Screening sample.

[m] Coagulation testing should be measured at Screening, Cycles 1, 2, and 3 predose (within 72 h prior to infusion) and 24 h post-infusion of AZD4573. For Cycles 4-8, predose (within 72 h of the infusion); the 24-h sample can be omitted unless clinically indicated. For Cycles 9+, on Day 1 of each cycle, an AZD4573 pre-infusion sample will be drawn within 72 h prior to infusion. A sample will also be drawn at the 30-day SFU. The Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF.

[n] Clinical chemistry should be measured at Screening, Cycles 1, 2, and 3 predose (within 72 h prior to infusion), and 24 h post-infusion of AZD4573. From Cycle 4 onwards, clinical chemistry testing should be measured predose (within 72 h prior to infusion) and (if clinically indicated) 24 h after the start of the infusion. A sample will also be drawn at the 30-day SFU. The investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF. Clinical chemistry tests do not need to be repeated before first dose if the first-dose visit is within 3 days of the Screening sample.
In addition, GLDH and CPK will be measured at Screening for all participants. If GLDH cannot be performed locally, LDH will be analysed locally and a serum sample must be collected for central retrospective GLDH analysis, which will be performed as applicable. Refer to the Laboratory Manual for details.
If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, potassium) and troponin must be done to coincide with the ECG testing.

[o] All participants will receive TLS prophylaxis during the intra-patient ramp up and be monitored for TLS during the first 24 hours post start of dose; this requirement will continue until they have received at least one AZD4573 dose at the target dose level (i.e., for at least the first 3 AZD4573 once-weekly doses). TLS monitoring will be performed at the following timepoints: predose AZD4573, 6 h after the start of the infusion, and 24 h (± 1 h) after the start of the infusion. Participants showing signs of clinical or laboratory TLS at 6 h after start of infusion must be admitted for in-patient TLS monitoring for a minimum of 24 h after the start of the infusion and monitored every 4 to 6 h during this time (or more frequently if clinically indicated). For each TLS monitoring timepoint, a TLS Monitoring page in the eCRF is to be filled out. Fluid balance must be monitored according to local institutional standards.

[p] Urine samples will be collected at the following timepoints: Screening, Cycles 1-8, predose AZD4573 (within 72 hours prior to infusion) and within approximately 2 hours after the end of infusion, Cycles 9+ on Day 1 of each cycle, predose AZD4573 and within approximately 2 hours after the end of infusion, and at the 30-day SFU.

[q] Pregnancy test to be performed at Screening (serum) and predose (serum or urine) on Cycle 1, Week 1, then once every 21 days (± 7 days) prior to initiating a new cycle and at the 30-day SFU visit. Additional testing may be performed at Investigator discretion (eg, in the event of suspected contraception failure).

[r] Lipase and amylase should be evaluated at Screening, Cycles 1-8 predose AZD4573 (within 72 hours prior to infusion), Cycles 9+, predose AZD4573 (within 72 hours prior to infusion) on Day 1 of each cycle, and at the 30-day SFU visit.

[s] In addition to hepatitis serology as specified, participants who are anti-HBc positive, or have a known history of HBV infection, should be monitored every 3 months with a quantitative PCR test for HBV DNA. In addition, any participants testing positive for any hepatitis serology must have PCR testing for verification purposes.

[t] CD4, CD8, CD19, CD16/NK and serum immunoglobulins (IgA, IgM, IgG) will be drawn at Screening, Day 1 (predose) of Cycles 2, 4, 7, 9, 13, 16, 19 and every 6 months thereafter (predose), and at the 30-day SFU.

[u] Plasma samples for PK analysis will be taken at the following time points: For Cycle 1, of Weeks 1-3 and Cycle 2, Day 1: predose (up to 2 h prior to AZD4573 and acalabrutinib administration) and 1 h (± 15 mins), 2 h (± 15 mins), 4 h (± 30 mins), 7 h (± 1 h), and 24 h (± 1 h) (ie, Day 2 of dosing, prior to acalabrutinib dosing) after the start of the infusion.

[v] Pharmacodynamic evaluations for AZD4573 blood samples will be collected at Cycle 1, Weeks 1 and 2 at predose (up to 2 h prior to dosing of either agent) and 2 h (± 15 mins), 4 h (± 30 mins), and 24 h (± 2 h) (ie, Day 2, but before acalabrutinib dosing) after the start of the infusion. Cycle 1 Week 3, predose (up to 2h prior to dosing), 2 h (± 15 mins), 4 h (± 30 mins),7 h (± 1 h), and 24 h (± 2 h) (ie, Day 2, but before acalabrutinib dosing) after the start of the infusion.

[w] Pharmacodynamic evaluations for acalabrutinib: blood samples (whole blood) are to be taken predose on Cycle 1, Week 1, (up to 2 h prior to dosing of either agent), and on Cycle 1, Week 4 (up to 2 h prior to dosing of either agent).

[x] CCI [redacted] Samples will be taken for all participants at Screening and Cycle 1, Weeks 1-3: predose (up to 2 h prior to dosing) and 4 h (± 30 mins), 7 h (± 1 h), and 24 h (± 1 h) after start of infusion. If the participant has CCI [redacted] at 24 h after start of infusion, samples will be drawn at 48 h (-2 h/+12 h prior to infusion), 96 h (- 2 h/+12 h prior to infusion), predose-the-following infusion (within 4 h prior to infusion), and at each point chemistry panel testing is being performed. CCI [redacted] with subsequent dosing with AZD4573, CCI [redacted] sampling should be performed the same as for Cycle 1, Weeks 1-3.

[y] Whole blood for exploratory CCI samples will be collected at Screening, Cycle 1, Weeks 1, 3, and 5 predose (within 2 h prior to dosing), Cycle 2, Days 1 and 15 predose (within 2 h prior to dosing), Day 1 of Cycles 3, 5, 6 and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[z] Whole Blood for CCI will be collected at Screening, Cycle 1, Weeks 1, 3, and 5 predose (within 2 h prior to dosing), Cycle 2, Days 1 and 15, predose (within 2 h prior to dosing), and on Day 1 of Cycles 3, 5, 6, and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[aa] Whole blood samples for CCI will be collected at Screening, Cycle 1, Weeks 1 and 3 predose (within 2 h prior to dosing), Cycle 2, Days 1 and 15, predose (within 2 h prior to dosing), Day 1 of Cycles 3, 5, and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[bb] Whole blood samples for CCI will be collected at Screening, Cycle 1, Weeks 1 and 3 predose (within 2 h prior to dosing), Cycle 2, Days 1 and 15 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[cc] Exploratory blood CCI Whole blood samples will be collected at Screening and Cycle 1 Weeks 1-3 at predose (within 2 h prior to dosing of either agent), 2 h (± 15 mins) and 24 h (± 2 h) after the start of the infusion (and prior to acalabrutinib dosing), and on Day 1 of Cycles 2, 3, 5, and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[dd] CCI sample for CCI isolation will be collected at Cycle 1, Week 1 predose.

[ee] An optional saliva sample for genomics initiative research will be taken from consenting participants prior to the first dose of IP. If for any reason the sample is not taken before dosing it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

[ff] A biopsy will be taken at disease progression for participants who consent. The disease progression sample may be taken at the SFU visit if not collected previously.

[gg] Bone marrow biopsy and aspirate: CCI

[hh] See Table 19 for schedule of disease assessments, including mandatory PET assessments. Disease assessments will be done by the Investigator using the Lugano Response Criteria for Non-Hodgkin's Lymphoma (Cheson et al 2014). Additional disease assessments may be performed as clinically indicated.

[ii] Acalabrutinib 100 mg oral capsule to be given twice per day.

[jj] AZD4573 is to be administered as an absolute (flat) dose, 2-h (± 15 mins) IV infusion on a once-weekly schedule.

[kk] Participant-reported drug administration for acalabrutinib needs to be done on every AZD4573 dosing day, ideally prior to dosing (± 24 h) and is also to be done after the last acalabrutinib capsule is taken and the leftover capsules returned to site. Drug accountability for acalabrutinib will occur every 2 weeks, (on an AZD4573 dosing day, ideally prior to dosing [± 24 h]).

[ll] If a participant is attending Cycle 9+ visits according to a modified schedule, in which AZD4573 is not infused and assessments are not performed every week, the Day 1 assessments should be performed at least once per cycle.

[mm] The End of Treatment visit is the last visit attended by the participant prior to the 30-Day SFU on the study. At this visit, the participant does not receive IMP and should undergo the applicable assessments associated with the Cycle and visit they have reached, plus those shown in the "Disease Assessment/End of Treatment" column of the SoA.

[nn] AZD4573 should be administered at least 5 days apart.

Abbreviations: ACTH = adrenocorticotropic hormone; BID = twice daily; CMV = cytomegalovirus; CPK = cyclin-dependent kinase; CSP = clinical study protocol; ECG = electrocardiogram; eCRF = electronic case report form; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; GLDH = glutamic dehydrogenase; Ig = immunoglobulin; CCI [redacted] LDH = lactate dehydrogenase; LTFU = long-term follow-up; CCI [redacted]; MUGA = multigated acquisition; CCI [redacted]; PCR = polymerase chain reaction; PK = pharmacokinetics; SFU = safety follow-up; SoC = standard of care; T4 = thyroxine; TLS = tumour lysis syndrome; TSH = thyroid-stimulating hormone.

Table 5 Schedule of Activities: Module 1 (AZD4573 with Acalabrutinib) Part B – Expansion

Assessment	Screen[a]	Cycle 1, Weeks 1-5 (includes intra-patient dose ramp up)	Cycle 2-8 (Cycle=21 Days)			Cycles 9+ (Cycle=21 days)[mm]	Disease assessment[b]/ End of Treatment[nn]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(±2 Days)	(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Informed consent[d]	X									Section 17.1.1
Inclusion/exclusion	X									Section 17.1.1
Medical history and demographics	X									Section 17.1.1
Physical examination[f]	X	X	X	X	X	X		X		Section 17.1.2
ECOG performance status	X	X	X	X	X	X		X		Section 17.1.4
Tumour biopsy sample (**mandatory**)	X									Section 17.10.2
Vital signs[e]	X	X	X	X	X	X (each infusion)		X		Section 17.1.3
Weight[f]	X	X	X			X		X		Section 17.1.3
B symptoms	X	X	X	X	X	X		X		Section 17.1.5

Assessment	Screen[a]	Cycle 1, Weeks 1-5 (includes intra-patient dose ramp up)	Cycle 2-8 (Cycle=21 Days)			Cycles 9+ (Cycle=21 days)[mm]	Disease assessment[b]/ End of Treatment[nn]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(±2 Days)	(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
12-lead ECG[g]	X	X	X			X		X		Section 17.1.8
CMV immunoglobulin M [IgM] and PCR[h]	X									Section 14.2, 17.1.6
Cardiac troponin[i]	X	X	X			X		X		Section 17.1.6
T4, cortisol, ACTH, and TSH[j]	X		X (Cycle 2 only)					X		Section 17.1.6
ECHO/MUGA[k]	X	As clinically indicated						X[k]		Section 17.1.7
Haematology[l]	X	X	X	X	X	X[l] (each infusions)		X		Section 17.1.6
Coagulation[m]	X	X	X	X	X	X[m]		X		Section 17.1.6
Clinical chemistry[n]	X	X	X	X	X	X[n] (each infusion)		X		Section 17.1.6

Assessment	Screen[a]	Cycle 1, Weeks 1-5 (includes intra-patient dose ramp up)	Cycle 2-8 (Cycle=21 Days)			Cycles 9+ (Cycle=21 days)[mm]	Disease assessment[b]/ End of Treatment[nn]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(±2 Days)	(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
TLS monitoring[o]		Weeks 1-3								Section 17.1.6
Urinalysis[p]	X	X	X	X	X	X		X		Section 17.1.6
Pregnancy testing (women of childbearing potential)[q]	X (Serum)	Week 1 (predose)	Once every 21 days (±7 days)					X		Section 17.1.6
Lipase/amylase[r]	X	X	X	X	X	X		X		Section 17.1.6
Hepatitis serology[s]	X		See footnote for schedule							Section 17.1.6 and Section 17.1.10.4
CD4, CD8, CD19, CD16/NK cell count[t]	X		See footnote for schedule					X		Section 17.1.7
Serum immunoglobulins (IgA, IgM, IgG)[t]	X		See footnote for schedule					X		Section 17.1.7

Assessment	Screen[a]	Cycle 1, Weeks 1-5 (includes intra-patient dose ramp up)	Cycle 2-8 (Cycle=21 Days)			Cycles 9+ (Cycle=21 days)[mm]	Disease assessment[b]/ End of Treatment[nn]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(±2 Days)	(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Concomitant medication	X	X	X	X	X	X (each infusion)	X	X	X	Section 15.11
Adverse event evaluation	X	X	X	X	X	X (each infusion)	X	X	X	Section 8.2
AZD4573/ acalabrutinib plasma PK[u]		Weeks 1-3	Cycle 2							Section 17.6
Pharmacodynamic samples (blood) for AZD4573[v]		Weeks 1-3[v]								Section 17.7
Pharmacodynamic samples (blood) for acalabrutinib[w]		Weeks 1 and 4, (predose)								Section 17.7
CCI [redacted]	X	Weeks 1-3	CCI [redacted]							Section 17.8
Whole blood for exploratory CCI [redacted] [b]	X	Weeks 1, 3, and 5	Cycles 2, 3, 5, 6, and 7		Cycle 2		X	(X)		Section 17.9.1

Assessment	Screen[a]	Cycle 1, Weeks 1-5 (includes intra-patient dose ramp up)	Cycle 2-8 (Cycle=21 Days)			Cycles 9+ (Cycle=21 days)[mm]	Disease assessment[b]/ End of Treatment[nn]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(±2 Days)	(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Whole Blood for CCI [z]	X	Weeks 1, 3, and 5	Cycles 2, 3, 5, 6, and 7		Cycle 2		X	(X)		Section 17.9.2
Whole blood samples for CCI [c]	X	Weeks 1 and 3	Cycles 2, 3, 5, and 7		Cycle 2		X	(X)		Section 17.9.3
Whole blood samples for CCI [dd]	X	Weeks 1 and 3	Cycle 2		Cycle 2		X	(X)		Section 17.9.4
Whole blood for CCI exploratory analysis[ee]	X	Week 1	Cycles 2, 3, 5, and 7				X	(X)		Section 17.9.5
Exploratory blood CCI	X	Weeks 1-3	Cycles 2, 3, 5, and 7				X	(X)		Section 17.9.6
CCI sample for CCI isolation[aa]	(X)	Week 1 (predose)								Section 17.10.4.1

Assessment	Screen[a]	Cycle 1, Weeks 1-5 (includes intra-patient dose ramp up)	Cycle 2-8 (Cycle=21 Days)			Cycles 9+ (Cycle=21 days)[mm]	Disease assessment[b]/ End of Treatment[nn]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(±2 Days)	(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Genomics Initiative saliva sample (optional)[ff]	(X)	Week 1 (predose)	(X)	(X)	(X)	(X)	(X)	(X)		Section 17.11
Bone marrow biopsy & aspirate[hh]	X						As clinically indicated and to confirm CR			Section 17.4.3 and Section 17.10.3
Tumour biopsy sample (optional)[gg]							At disease progression	(X)[gg]		Section 17.10.5.1
Disease assessment[b] and radiologic scans[ii]	X	See Table 19 for schedule						X		Section 17.4.2
Acalabrutinib oral, BID[jj]		Twice daily (from Cycle 1 Week 1 to end of treatment)								Section 15.1
AZD4573 intravenous[kk]		Once weekly (from Cycle 1, Week 1 to end of treatment)[oo]								Section 15.1
Acalabrutinib drug accountability[ll]		X	X	X	X	X				Section 15.8
Disease progression follow-up (SoC)									X	Section 17.1.9.2

Assessment	Screen[a]	Cycle 1, Weeks 1-5 (includes intra-patient dose ramp up)	Cycle 2-8 (Cycle=21 Days)			Cycles 9+ (Cycle=21 days)[mm]	Disease assessment[b]/ End of Treatment[nn]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(±2 Days)	(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Survival follow-up									X	Section 17.1.9.3

[a] Screening tests should be performed within 30 days before the first administration of study drug, unless otherwise indicated.

[b] Disease assessments will be done by the Investigator using the Lugano Response Criteria for Non-Hodgkin's Lymphoma (Cheson et al 2014). Additional disease assessments may be performed as clinically indicated.

[c] The SFU visit will be performed 30 days (±7 days) after the last dose of all study drug. Tumour assessments will be repeated at this visit if they have not been performed within 9 weeks if the participant discontinued before or during Week 26, or 12 weeks if the participant discontinued after Week 26.

[d] Informed consent must be obtained ≤ 30 days before the first dose of study drug and must be obtained before any protocol-defined screening procedures are done.

[e] Vital signs (blood pressure, pulse rate, temperature) will be assessed after the participant has rested for at least 10 mins. Blood pressure and pulse rate will be measured at Screening, and on Day 1 of Cycle 1, Weeks 1-3 at the following timepoints: predose (up to 2 h prior to infusion), 1 h after the start of the infusion (± 10 mins), at end of infusion (up to 10 mins post dose) and then 4 h (± 30 mins) and 6 h (± 30 mins) after start of infusion, from Cycle 1 Week 4 onwards, at predose (up to 30 mins prior to infusion), at the end of infusion (up to 30 mins post dose), and at the 30-day SFU. Temperature to be taken pre-infusion (up to 2 h prior to all infusions).

[f] As the study is intended to recruit adults, height should only be measured at Screening. Weight to be measured at Screening, prior to infusion on Day 1 of each cycle, and at the 30-day SFU visit.

[g] Participants should be in semi-supine position and resting for ≥ 10 mins before the ECGs. Single ECGs for local and central analysis are required at Screening and at the following timepoints: for Cycle 1, Weeks 1-5 and Cycle 2 Day 1 predose (at the day of infusion prior to infusion) and within 30 mins of the end of infusion; for Cycles 3+ on Day 1 within 30 mins after the end of infusion, and at the 30-day SFU visit.

[h] All subjects will have CMV testing at Screening including serology testing for CMV immunoglobulin (Ig)G and CMV IgM and CMV DNA PCR testing

[i] Cardiac troponin measurements are required at the following timepoints: Screening, Cycle 1, Weeks 1-5, predose (within 72 hours prior to infusion) and at 24 h after the start of the infusion, and Cycles 2+ on Day 1 of each cycle, predose (within 72 hours prior to infusion), and at the 30-day SFU visit. Note: either a troponin I or troponin T assay can be used per SoC at the respective hospital. If the hospital has both a SoC troponin I and troponin T assay available, the investigator shall use only one consistently for the duration of the study.

[j] T4, cortisol, ACTH, and TSH to be taken at Screening, predose (within 72 hours prior to infusion) on Cycle 2, Day 1, and at the 30-day SFU.

[k] ECHO should be done at Screening and within 14 days after an abnormal ECG finding (eg, T-wave inversion/flattening) or as soon as possible when clinically indicated. If an ECHO cannot be taken, a MUGA scan to assess LVEF will be done. In case of any T-wave abnormality, the ECHO (or MUGA) should be repeated at the 30-day follow-up visit to address the question of recovery, during the off-treatment period.

[l] Haematology testing should be measured at Screening, Cycles 1, 2, and 3 predose (within 72 h prior to infusion) and 24 h after the start of the infusion. From Cycle 4 onwards, haematology testing should be predose (within 72 h prior to infusion) and (if clinically indicated) 24 h after the start of the infusion. A sample will also be drawn at the 30-day SFU. The Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF. Haematology tests do not need to be repeated before first dose if the first-dose visit is within 3 days of the Screening sample.

[m] Coagulation testing should be measured at Screening, Cycles 1, 2, and 3 predose (within 72 h prior to infusion) and 24 h post-infusion of AZD4573. For Cycles 4-8, predose (within 72 h prior to infusion); the 24-h sample can be omitted unless clinically indicated. For Cycles 9+, on Day 1 of each cycle, an AZD4573 pre-infusion sample will be drawn within 72 h prior to infusion. A sample will also be drawn at the 30-day SFU. The Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF.

[n] Clinical chemistry should be measured at Screening, Cycles 1, 2, and 3 predose (within 72 h prior to infusion), and 24 h post-infusion of AZD4573. From Cycle 4 onwards, clinical chemistry testing should be measured predose (within 72 h prior to infusion) and (if clinically indicated) 24 h after the start of the infusion. A sample will also be drawn at the 30-day SFU. The investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF. Clinical chemistry tests do not need to be repeated before first dose if the first-dose visit is within 3 days of the Screening sample.
In addition, GLDH and CPK will be measured at Screening for all participants. If GLDH cannot be performed locally, LDH will be analysed locally and a serum sample must be collected for central retrospective GLDH analysis, which will be performed as applicable. Refer to the Laboratory Manual for details.
If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, potassium) and troponin must be done to coincide with the ECG testing.

[o] All participants will receive TLS prophylaxis during the intra-patient ramp up and be monitored for TLS during the first 24 hours post start of dose; this requirement will continue until they have received at least one AZD4573 dose at the target dose level (i.e., for at least the first 3 AZD4573 once-weekly doses). TLS monitoring will be performed at the following timepoints: predose AZD4573, 6 h after the start of the infusion, and 24 h (± 1 h) after the start of the infusion. Participants showing signs of clinical or laboratory TLS at 6 h after start of infusion must be admitted for in-patient TLS monitoring for a minimum of 24 h after the start of the infusion and monitored every 4 to 6 h during this time (or more frequently if clinically indicated). For each TLS monitoring timepoint, a TLS Monitoring page in the eCRF is to be filled out. Fluid balance must be monitored according to local institutional standards.

[p] Urine samples will be collected at the following timepoints: Screening, Cycles 1-8, predose AZD4573 (within 72 hours prior to infusion) and within approximately 2 hours after the end of infusion, Cycles 9+ on Day 1 of each cycle, predose AZD4573 and within approximately 2 hours after the end of infusion, and at the 30-day SFU.

[q] Pregnancy test to be performed at Screening (serum) and predose (serum or urine) on Cycle 1, Week 1, then once every 21 days (± 7 days) prior to initiating a new cycle and at the 30-day SFU visit. Additional testing may be performed at Investigator discretion (eg, in the event of suspected contraception failure).

[r] Lipase and amylase should be evaluated at Screening, Cycles 1-8 predose AZD4573 (within 72 hours prior to infusion), Cycles 9+, predose AZD4573 (within 72 hours prior to infusion) on Day 1 of each cycle, and at the 30-day SFU visit.

[s] In addition to hepatitis serology as specified, participants who are anti-HBc positive, or have a known history of HBV infection, should be monitored every 3 months with a quantitative PCR test for HBV DNA. In addition, any participants testing positive for any hepatitis serology must have PCR testing for verification purposes.

[t] CD4, CD8, CD19, CD16/NK and serum immunoglobulins (IgA, IgM, IgG) will be drawn at Screening, Day 1 (predose) of Cycles 2, 4, 7, 9, 13, 16, 19 and every 6 months thereafter (predose), and at the 30-day SFU.

[u] Plasma samples for PK analysis will be taken at the following time points: For Cycle 1, of Weeks 1-3 and Cycle 2, Day 1: predose (up to 2 h prior to AZD4573 and acalabrutinib administration), 2 h (± 15 mins), and 4 h (± 30 mins) after the start of the infusion.

[v] Pharmacodynamic evaluations for AZD4573 blood samples will be collected at Cycle 1, Weeks 1-3 predose (up to 2 h prior to dosing of either agent) and 2 h (± 15 mins), 4 h (± 30 mins), 7 h (± 1 h), and 24 h (± 2 h) (ie, Day 2, but before acalabrutinib dosing) after the start of the infusion.

w Pharmacodynamic evaluations for acalabrutinib: blood samples (whole blood) are to be taken predose on Cycle 1, Week 1, (up to 2 h prior to dosing of either agent), and on Cycle 1, Week 4 (up to 2 h prior to dosing of either agent).

x CCI [redacted] Samples will be taken for all participants at Screening and Cycle 1, Weeks 1-3: predose (within 2 h prior to dosing) and 4 h (± 30 mins), 7 h (± 1 h), and 24 h (± 1 h) after start of infusion. If the participant has CCI [redacted] at 24 h after start of infusion, samples will be drawn at 48 h (-2 h/+12 h prior to infusion), 96 h (- 2 h/+12 h prior to infusion), predose-the-following infusion (within 4 h prior to infusion), and at each point chemistry panel testing is being performed. For any CCI [redacted] with subsequent dosing with AZD4573, CCI [redacted] sampling should be performed the same as for Cycle 1, Weeks 1-3.

y Exploratory blood CCI [redacted] Whole blood samples will be collected at Screening and Cycle 1 Weeks 1-3 at predose (within 2 h prior to dosing of either agent), 2 h (± 15 mins) and 24 h (± 2 h) after the start of the infusion (and prior to acalabrutinib dosing), and on Day 1 of Cycles 2, 3, 5 and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

z Whole Blood for CCI [redacted] will be collected at Screening, Cycle 1, Weeks 1, 3, and 5 predose (within 2 h prior to dosing), Cycle 2, Days 1 and 15, predose (within 2 h prior to dosing), and on Day 1 of Cycles 3, 5, 6, and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

aa CCI [redacted] sample for CCI [redacted] isolation will be collected at Cycle 1, Week 1 predose.

bb Whole blood for exploratory CCI [redacted] will be collected at Screening, Cycle 1, Weeks 1, 3, and 5 predose (within 2 h prior to dosing), Cycle 2, Days 1 and 15 predose (within 2 h prior to dosing), Day 1 of Cycles 3, 5, 6 and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

cc Whole blood samples for CCI [redacted] will be collected at Screening, Cycle 1, Week 1 predose (within 2 h prior to dosing), Cycle 1, Week 3, predose (within 2 h prior to dosing) and 24 h (± 2 hours), Cycle 2, Days 1 and 15, predose (within 2 h prior to dosing), Day 1 of Cycles 3, 5, and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

dd Whole blood samples for CCI [redacted] will be collected at Screening, Cycle 1, Week 1 predose (within 2 h prior to dosing), Cycle 1, Week 3, predose (within 2 h prior to dosing), Cycle 2, Days 1 and 15 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

ee Whole blood for CCI [redacted] exploratory analysis samples will be collected at Screening, Cycle 1, Week 1 predose (within 2 h prior to dosing), Day 1 of Cycles 2, 3, 5, and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

ff An optional saliva sample for genomics initiative research will be taken from consenting participants prior to the first dose of IP. If for any reason the sample is not taken before dosing it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

gg A biopsy will be taken at disease progression for participants who consent. The disease progression sample may be taken at the SFU visit if not collected previously.

hh Bone marrow biopsy and aspirate: CCI [redacted]

ii See Table 19 for schedule of disease assessments, including mandatory PET assessments. Disease assessments will be done by the Investigator using the Lugano Response Criteria for Non-Hodgkin's Lymphoma (Cheson et al 2014). Additional disease assessments may be performed as clinically indicated.

jj Acalabrutinib 100 mg oral capsule to be given twice per day.

[kk] AZD4573 is to be administered as an absolute (flat) dose, 2-h (± 15 mins) IV infusion on a once-weekly schedule.

[ll] Participant-reported drug administration for acalabrutinib needs to be done on every AZD4573 dosing day, ideally prior to dosing (± 24 h) and is also to be done after the last acalabrutinib capsule is taken and the leftover capsules returned to site. Drug accountability for acalabrutinib will occur every 2 weeks, (on an AZD4573 dosing day, ideally prior to dosing [± 24 h]).

[mm] If a participant is attending Cycle 9+ visits according to a modified schedule, in which AZD4573 is not infused and assessments are not performed every week, the Day 1 assessments should be performed at least once per cycle.

[nn] The End of Treatment visits is the last visit attended by the participant prior to the 30-Day SFU on the study. At this visit, the participant does not receive IMP and should undergo the applicable assessments associated with the Cycle and visit they have reached, plus those shown in the "Disease Assessment/End of Treatment" column of the SoA.

[oo] AZD4573 should be administered at least 5 days apart.

Abbreviations: ACTH = adrenocorticotropic hormone; BID = twice daily; CMV = cytomegalovirus; CPK = cyclin-dependent kinase; CSP = clinical study protocol; ECG = electrocardiogram; eCRF = electronic case report form; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; GLDH = glutamic dehydrogenase; Ig = immunoglobulin; CCI [redacted] LDH = lactate dehydrogenase; LTFU = long-term follow-up; CCI [redacted]; MUGA = multigated acquisition; CCI [redacted]; PCR = polymerase chain reaction; PK = pharmacokinetics; SFU = safety follow-up; SoC = standard of care; T4 = thyroxine; TLS = tumour lysis syndrome; TSH = thyroid-stimulating hormone.

11 INTRODUCTION – MODULE 1

11.1 Study Rationale – Module 1

DLBCL

Preliminary anti-tumour activity has been observed with AZD4573 as monotherapy in participants with relapsed or refractory (r/r) haematological malignancies in the ongoing Phase I, FTIH, dose-escalation study (D8230C00001; see Section 2.2.6), in which best overall responses included one with CR, one with PR, and 4 with SD in participants with DLBCL. In addition, signs of clinical activity were observed in DLBCL and CLL participants as short, repeated tumour size reductions after each AZD4573 administration of up to 49% of the tumour volume, but with tumour regrowth during off-treatment periods. This pattern was observed over a range of dose levels and points to the need for combination therapies directed to sustaining the potential clinical benefit with AZD4573 treatment. Data with AZD4573 in combination with acalabrutinib in an activated B-cell (ABC) DLBCL xenograft model have shown an increase in both the magnitude and duration of anti-tumour response compared with either single agent alone (see Section 2.2.5.1). Inhibition of the BTK pathway with acalabrutinib causes an increase of certain BCL2 family pro-apoptotic proteins, like Bim, (Deng 2017a, Deng et al 2017b, Sasi et al 2019) pushing the cancer cells closer to their apoptotic threshold, a mechanism known as 'apoptotic priming' (NCCN 2021, Ni Chonghaile et al 2011). With the addition of AZD4573 following a short lead-in of acalabrutinib, both the magnitude and duration of anti-tumour response is increased compared to either monotherapy as evidenced- by more rapid and robust cleavage of caspase-3 and delayed time to tumour regrowth following treatment cessation (Patent WO2019/058348; data on file).

Given acalabrutinib's previously demonstrated activity in B-cell malignancies, its initial demonstration of clinical activity in the difficult-to-treat population of r/r DLBCL as monotherapy, and mechanism of action (non-overlapping with CDK9 inhibitors), combination therapy with acalabrutinib and AZD4573 may reasonably be expected to yield greater clinical benefit than with either agent alone.

MZL

Marginal zone lymphoma (MZL) is a rare form of NHL with an indolent course requiring intermittent treatment and surveillance. While localised disease may be treated curatively, treatment for advanced MZL includes anti-CD20 therapy, chemotherapy, or chemoimmunotherapy, however, most patients relapse after first-line treatment (Denlinger et al 2018; Zucca et al 2020). While lenalidomide, in combination with rituximab, and the first generation BTK inhibitor ibrutinib as monotherapy are approved in the United

States for treatment of patients with previously treated MZL (ibrutinib as an accelerated approval for treatment of patients with MZL requiring systemic therapy and who have received at least one prior anti-CD20-based therapy), there remains an unmet need for treatment of patients with advanced MZL. Both National Comprehensive Cancer Network (NCCN) and ESMO guidelines recommend enrolment of patients with advanced disease into clinical trials (NCCN 2021, Zucca et al 2020).

Expression of the anti-apoptotic MCL-1 has been evaluated in human B-cell lymphomas, including MZL (Cho-Vega et al 2004). MCL-1 was expressed across different subtypes of MZL: in 4 of 5 (80%) nodal and splenic marginal zone B-cell lymphoma, and 4 of 11 (36%) extranodal marginal zone B-cell lymphoma of MALT type.

Preliminary data from the ongoing Phase IB/II clinical study evaluating acalabrutinib as monotherapy in 40 participants with r/r MZL (Study ACE-LY-003) indicate an objective response rate (ORR) of 53.85% (11.54% CR, 42.31% PR) (data on file, AstraZeneca). These findings are similar to those reported in the Phase II open-label study which supported accelerated FDA approval of ibrutinib in participants with MZL: among 60 evaluable with a median of 2 prior treatments (range 1-9), the ORR was 48% (3% CR, 45% PR) (Noy et al 2017).

Given the demonstrated activity of BTK inhibitors in MZL (Lue et al 2020), their relatively well-tolerated safety profile, and a mechanism of action that is non-overlapping with CDK9 inhibitors, it is hypothesised that combination therapy with AZD4573 and acalabrutinib may yield greater clinical benefit than with either agent alone in patients with MZL.

In Part A, this module will initially explore once-weekly administration of AZD4573 in combination with oral acalabrutinib 100 mg twice daily and will enrol participants with r/r DLBCL or r/r MZL who have failed prior therapy(ies), are not eligible for curative treatment options, and for whom there is no standard therapy available.

In Part B, separate expansion cohorts for DLBCL GCB and non-GCB subtypes will be opened at the RP2D. For both Part A and Part B, diagnosis must be confirmed by biopsy and cell of origin subtype characterised locally prior to enrolment. Tumour tissue must also be available for sending to AstraZeneca for central cell of origin testing (archival tissue or fresh biopsy, depending on the study part). A participant will be enrolled based on a prior pathology report.

A further expansion in MZL participants may be opened by a protocol amendment, based on emerging clinical data.

11.2 Acalabrutinib Background

For background information on AZD4573, please refer to Section 2.2.

Acalabrutinib is also known as ACP-196 and Calquence®. Calquence is approved in the United States and is either approved or under regulatory assessment in other countries as:

- Monotherapy for the treatment of adult patients with MCL who have received at least one prior therapy.
- Monotherapy and in combination with obinutuzumab for the treatment of adult patients with CLL or SLL.

Acalabrutinib is a selective, irreversible small molecule BTK inhibitor. In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Acalabrutinib and its major metabolite ACP-5862 inactivate BTK by forming a covalent bond with a cysteine residue in the kinase active site. This leads to inhibition of signaling through the B-cell receptor (BCR) in sensitive cells. In nonclinical and clinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and survival.

11.2.1 Clinical Experience with Acalabrutinib

As of 30 October 2020, more than 6000 participants have participated in acalabrutinib clinical studies, with approximately 4500 participants receiving acalabrutinib as monotherapy or in combination with other agents in the oncology program. Clinical studies have included participants with haematological malignancies, solid tumours, or rheumatoid arthritis, and participants who are healthy subjects or those with mild to moderate hepatic impairment.

No DLTs have been identified in any studies for acalabrutinib monotherapy and very few with acalabrutinib (given as 100 mg twice daily) in combination with other agents. Important identified risks for acalabrutinib are haemorrhage, atrial fibrillation/flutter, infections, cytopenias, and second primary malignancies. Transaminase elevations (ALT/AST) are considered an important potential risk when the drug is given as monotherapy.

Efficacy data summarised below are based on two pivotal clinical studies in CLL/SLL (ACE-CL-007 and ACE-CL-309) and 3 supportive clinical studies in CLL/SLL (ACE-CL-001, ACE-CL-003, and 15-H-0016). Assessment of overall response was based on modified International Workshop on Chronic Lymphocytic Leukemia (iwCLL) response criteria (Hallek et al 2008) for CLL/SLL participants, with incorporation of the clarification for treatment-related lymphocytosis (Cheson et al 2012).

Ongoing Phase III Pivotal Studies in CLL

Efficacy data for acalabrutinib monotherapy (100 mg twice daily) as well as efficacy data for the combination of acalabrutinib 100 mg twice daily with obinutuzumab from two pivotal ongoing Phase III studies in previously untreated CLL (ACE-CL-007; CCI

CCI and r/r CLL (ACE-CL-309; CCI

Study ACE-CL-309 enrolled and randomised a total of 310 participants CCI Acalabrutinib demonstrated a 69% reduction in risk of Independent Review Committee (IRC)-assessed disease progression or death compared with idelalisib + rituximab /bendamustine and rituximab (IR/BR; hazard ratio [HR] = 0.31 [95% CI: 0.20, 0.49], $p < 0.0001$). The clinical benefit with acalabrutinib was further demonstrated by a clinically relevant improvement in DoR for acalabrutinib compared with IR/BR, both by IRC assessment (HR = 0.33) and Investigator-assessment (HR = 0.20), and a significant prolongation of time to next treatment (TTNT) for acalabrutinib compared with IR/BR (HR = 0.35; $p < 0.0001$).

Study ACE-CL-007 enrolled and randomised a total of 535 participants CCI Acalabrutinib + obinutuzumab demonstrated a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab + chlorambucil, with a 90% reduction in risk of disease progression or death (HR = 0.10 [95% CI: 0.06, 0.17]; $p < 0.0001$). Acalabrutinib monotherapy also demonstrated a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab + chlorambucil, with an 80% reduction in risk of disease progression or death (HR = 0.20 [95% CI: 0.13, 0.30]; $p < 0.0001$). The clinical benefit with acalabrutinib was further demonstrated by a significant prolongation of TTNT compared with obinutuzumab + chlorambucil for both acalabrutinib + obinutuzumab (HR=0.14 [95% CI: 0.08, 0.26]; $p < 0.0001$) and acalabrutinib monotherapy (HR = 0.24 [95% CI: 0.15, 0.40]; $p < 0.0001$).

Supportive Studies

Efficacy data for acalabrutinib monotherapy (100 mg twice daily) as well as efficacy data for the combination of acalabrutinib 100 mg twice daily with obinutuzumab from 3 supportive ongoing studies in CLL: ACE-CL-001 CCI , 15-H-0016 CCI , and ACE-CL-003 CCI

A total of 300 participants received acalabrutinib in the 3 supportive studies, including 166 r/r participants and 134 previously untreated participants. The efficacy results in the supportive studies in participants with r/r and previously untreated CLL are consistent with the results of the pivotal studies. Investigator-assessed ORR in all studies ranged from 87.5% to 100%. Across all cohorts, 6% of participants achieved CR, and 85% of participants achieved PR as a best response. The median DoR (PR or better) was not reached in any of the cohorts (range: 0.07+ to 51.3+ months).

Acalabrutinib has also been preliminarily assessed as monotherapy in participants with r/r de novo DLBCL (Denlinger et al 2018, Dyer et al 2018). In the latter study, among 21 participants enrolled, an ORR of 24% (19% CRs) was observed. CCI

CCI

11.3 Benefit/Risk Assessment – Module 1

For more detailed information about the known and expected benefits and potential risks of AZD4573, please refer to Section 2.3 CCI

More detailed information about the known and expected benefits and potential risks of AZD4573 and acalabrutinib in combination are summarised below. CCI

As outlined in Section 2.2.6 and in Section 11.3.2, AZD4573 has shown preliminary activity in participants with DLBCL in the ongoing FTIH study (D8230C00001). Given the demonstrated activity of BTK inhibitors in B-cell malignancies, their relatively well-tolerated safety profile, and mechanism of action (non-overlapping with CDK9 inhibitors), combination therapy may reasonably be expected to yield greater clinical benefit than with either agent alone.

Given acalabrutinib's previously demonstrated activity in B-cell malignancies, its initial demonstration of clinical activity as monotherapy in the difficult-to-treat population of r/r DLBCL and r/r MZL, and mechanism of action (Section 11.2), combination therapy with AZD4573 and acalabrutinib may reasonably be expected to yield greater clinical benefit than with either agent alone. This is supported by positive results in nonclinical studies with AZD4573 and acalabrutinib that demonstrated an increase in both the magnitude and duration of anti-tumour response compared with either single agent alone (Section 2.2.5.1 and Section 11.3.2).

11.3.1 Risk Assessment

Important identified risks for acalabrutinib are:

- Haemorrhage
- Atrial fibrillation

- Infections
- Cytopenias
- Second primary malignancies

Potential for overlapping toxicities between AZD4573 and acalabrutinib include TLS, haemorrhage, cytopenias, infection including hepatitis B reactivation, gastrointestinal toxicities (nausea, vomiting, and diarrhoea), and liver enzyme abnormalities (Grade 3 and Grade 4 transaminase elevations) with the important potential risk of hepatic injury (Table 6).

Detailed descriptions of safety concerns and management are provided in Section 17.1.10. Investigators should be particularly alert to the possibility of TLS, significant bleeding and infection, including opportunistic and fungal infections, and care must be taken to monitor platelets and neutrophil counts in accordance with the SoA and more frequently as clinically indicated. 'Rescue medications', including platelet transfusions and granulocyte-colony-stimulating factor (G-CSF), are permitted at any time during the study, at the discretion of the Investigator. Specific and detailed guidance is also given in this protocol regarding the management of events of hepatic dysfunction or toxicity.

Several measures, including project-specific, safety-related inclusion/exclusion criteria, physical examinations, evaluation of DLTs and AEs/SAEs, and laboratory testing throughout the study and study treatment modifications and toxicity management guidelines have been incorporated into the study protocol to mitigate any potential or identified risks associated with combining these agents. For further information, refer to the reference safety information for AZD4573 and/or Calquence accordingly.

Table 6 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention (s) AZD4573 and Acalabrutinib		
Headache	Headache is an identified risk for acalabrutinib.	Refer to Section 17.1.10.1
Diarrhoea	Diarrhoea is an identified risk for AZD4573 and acalabrutinib.	Refer to Section 17.1.10.2
Nausea and vomiting	Nausea and/or vomiting are identified risks for AZD4573 and acalabrutinib.	Refer to Section 17.1.10.3
Hepatitis B reactivation	Serious or life-threatening reactivation of viral hepatitis have been reported in patients treated with acalabrutinib.	Refer to Section 17.1.10.4

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Progressive multifocal leukoencephalopathy (PML)	Cases of PML have been reported in patients treated with acalabrutinib.	Refer to Section 17.1.10.5
Haemorrhage	Bleeding events, some fatal, including central nervous system, respiratory, and gastrointestinal haemorrhage, have been reported in patients treated with acalabrutinib.	Refer to Section 17.1.10.6
Infections	Serious infections, including fatal events, have been reported in patients treated with acalabrutinib and it is an important identified risk. Infection is an important potential risk for AZD4573.	Refer to Section 17.1.10.7
Cytopenia	Haematological toxicities including neutropenia, anaemia, and thrombocytopenia have occurred in patients treated with acalabrutinib, and neutropenia is an important identified risk for participants treated with AZD4573 or acalabrutinib.	Refer to Section 17.1.10.8
Liver chemistry test abnormalities	Grade 3 and Grade 4 transaminase elevations with bilirubin increase are an important potential risk for participants treated with acalabrutinib, and an important identified risk for participants treated with AZD4573.	Refer to Section 17.1.10.9
Hepatic injury	Events of hepatotoxicity have been reported in clinical studies with acalabrutinib however, no causal relationship has been established. Subjects with hepatotoxicity should be monitored for resolution, and dose modification or interruption of acalabrutinib may be indicated. In addition, subjects should be managed according to study protocols as well as institutional guidelines with supportive care.	Refer to Section 17.1.10.9
Tumour lysis syndrome (TLS)	TLS is an important identified risk for AZD4573 and an identified risk for acalabrutinib.	Refer to Section 17.1.10.10
Second primary malignancies	Second primary malignancies, including non-skin cancers, have been reported in patients treated with acalabrutinib.	Refer to Section 17.1.10.11
Atrial fibrillation/flutter	Atrial fibrillation/flutter have been reported in patients treated with acalabrutinib. Heart rate increase is a potential risk for AZD4573, and cases of atrial fibrillation have occurred in participants treated with AZD4573.	Refer to Section 17.1.10.12

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Infection/Bone marrow toxicity with peripheral effect/ lymphoid tissue hypocellularity	Infection / bone marrow toxicity with peripheral effect / lymphoid tissue hypocellularity is an important potential risk for AZD4573.	Refer to Section 17.1.10.13
Pancreatic and Cortical Adrenal Injury (as well as Surveillance for Renal, Thymus, and Spleen Toxicity)	Pancreatic injury and cortical adrenal injury are potential risks for AZD4573 based on preclinical observations.	Refer to Section 17.1.10.14
Drug-drug interactions	Specific drug-drug interaction studies have not yet been performed for AZD4573. Acalabrutinib may be affected by agents that reduce gastric acidity (antacids or proton-pump inhibitor).	Refer to Section 17.1.10.15
Myocardial ischaemia	Myocardial ischaemia and increased heart rate are considered potential risks for AZD4573.	Refer to Section 17.1.10.16
Study Procedures		
Infusion site reactions	As with other drugs administered intravenously, local infusion site reactions (eg, infusion pain, infusion site reaction, skin or vein irritation) may occur.	Refer to Section 17.1.10.17

The Investigator sites participating in this study are all experienced oncology centres and are well equipped for treating patients with relapsed and refractory disease and in the management of haematological toxicities. Furthermore, the protocol has dose reductions and dose interruption criteria to also allow for the management of any potential dose-related toxicity.

11.3.2 Benefit Assessment

Preliminary anti-tumour activity has been observed with AZD4573 as monotherapy in participants with r/r haematological malignancies in the ongoing Phase I, FTIH, dose-escalation study (D8230C00001; see Section 2.2.6). Best overall responses in participants with DLBCL (n=17) included 1 with CR, 1 with PR, and 4 with SD.

The addition of agents which in combination could provide more continuous anti-tumour activity may reasonably be expected to significantly enhance clinical benefit with manageable changes to risk. Acalabrutinib, a BTK inhibitor like ibrutinib, has been shown to inhibit proliferation and induce apoptosis in B-cell malignancies (Davis et al 2010, Harrington et al 2016). The latter is likely due to the ability of BTK inhibitors to increase

certain pro-apoptotic BCL2 family proteins, like Bim, (Deng 2017a, Deng et al 2017b, Sasi et al 2019) pushing the cancer cells closer to their apoptotic threshold, a mechanism known as 'apoptotic priming' (NCCN 2021, Ni Chonghaile et al 2011). Capitalising on this apoptotic priming, addition of AZD4573 following a short lead-in of acalabrutinib in the OCI-LY10 DLBCL xenograft model causes an increase in both the magnitude and duration of anti-tumour response, compared to either monotherapy, as demonstrated by more rapid and robust cleavage of caspase-3 and delayed time to tumour regrowth following treatment cessation (Patent WO2019/058348; data on file, Astra Zeneca).

Acalabrutinib is a highly selective, potent, covalent inhibitor of BTK with minimal off-target activity leading to a safety profile that may be attractive for combination strategies. It is therefore regarded as a promising agent for combination with AZD4573 in treatment of participants with DLBCL or MZL who have failed previously approved regimens

11.3.3 Overall Benefit/Risk Conclusion

Eligible participants will be r/r to prior treatments for their disease and considered to have no alternative treatment options available to them. Furthermore, participants will have varying levels of disease burden at study entry and almost certainly have acquired mutations as part of their disease course. Therefore, there is no guarantee that any participant will derive clinical benefit during this study.

AstraZeneca believes the anticipated benefits that may be afforded to participants with r/r haematological malignancies currently outweigh the identified and potential risks associated with AZD4573 in combination with acalabrutinib.

As described, the study design aims to minimise risks and build on the preliminary efficacy seen to date in the ongoing FTIH study (D8230C00001), reflecting clinical responses in a r/r participant population. Thus, the benefit/risk assessment for this Phase I/II combination study is considered acceptable for participants for whom there is no alternative standard therapy.

For an assessment of benefit and risks pertaining to the conduct of this study during the COVID-19 pandemic, refer to Appendix A 11.

12 OBJECTIVES AND ENDPOINTS – MODULE 1

Objectives and Endpoints for Part A and Part B are outlined in Table 7.

Table 7 Objectives and Endpoints – Module 1

Objectives	Endpoints
Primary	
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
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 participants who have a tumour response (CR and PR)[a]
Secondary	
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

Objectives	Endpoints
• 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
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
Exploratory	
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

Objectives	Endpoints
Part A and B	
• Assess the PD of AZD4573 CCI [redacted]	• CCI [redacted]
• Assess CCI [redacted]	• CCI [redacted]
• To evaluate CCI [redacted]	• CCI [redacted]
• To CCI [redacted]	• CCI [redacted]

[a] By Investigator assessment; however, if preliminary results suggest a major advantage over available therapy, AstraZeneca will consult with relevant Health Authorities to agree on modifications to the protocol and will conduct blinded independent central review of ORR (see Section 11.3.1).

Abbreviations: BID = twice daily; CCI [redacted] 9; CR = complete response; DLT = dose-limiting toxicity; DoR = duration of response; ECG = electrocardiogram; CCI [redacted] CCI [redacted] MTD = maximum tolerated dose; ORR = objective response rate; OS = overall survival; CCI [redacted] PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; CCI [redacted]; CCI [redacted] RP2D = recommended Phase II dose; TTR = time to response.

13 STUDY DESIGN – MODULE 1

Module 1 will enrol participants at approximately 30 sites in approximately 10 countries.

13.1 Overall Design

This is a modular, multicentre, open-label, non-randomised, Phase I/II, dose-setting and expansion study including an intra-patient ramp up.

In Part A (dose setting), this study module will enrol participants with r/r DLBCL or r/r MZL who have failed prior therapy(ies), are not eligible for curative treatment options, for whom there is no standard therapy available, and will initially explore once-weekly administration of AZD4573 at up to 3 target dose levels in combination with oral acalabrutinib 100 mg twice daily. The primary objective of Part A will be to identify the MTD and/or RP2D for further evaluation in Part B.

A 5-week DLT-assessment period will incorporate the whole of Cycle 1 in Part A, including the dose ramp up and the first 3 weeks at the target dose.

In Part B (expansion), separate expansion cohorts for participants with GCB and non-GCB DLBCL subtypes will be opened at the RP2D.

For both Part A and Part B, diagnosis must be confirmed by biopsy and cell of origin subtype characterised locally prior to enrolment and must be immunohistologically characterised. Tumour tissue must also be available for sending to AstraZeneca for central cell of origin testing (archival tissue or fresh biopsy, depending on the study part). A participant will be enrolled based on a prior pathology report.

Part A: Dose Setting (DLBCL and MZL)

Cycle 1 consists of 5 weeks, including an intra-patient dose ramp up (first 3 AZD4573 administrations) to achieve the target dose level, and 3 weeks of observation at the target dose level (5-week DLT-assessment period in total). Subsequent cycles are 21 days (3 weeks) with once-weekly IV administration of AZD4573 in combination with oral administration of acalabrutinib 100 mg twice daily continuously. Acalabrutinib (100 mg twice daily) is taken orally continuously from Day 1 of Cycle 1 Week 1. AZD4573 should be administered at least 5 days apart. For information on dosing schemes and cycle lengths, see Figure 5 and Table 8.

Table 8 Dosing Schedule – Module 1

Dose/Schedule	DLT-Assessment Period[a]	Cycle Length
Dose level -1; target dose: 6 mg Cycle 1, Weeks 1 to 5 (includes intra-patient ramp up): AZD4573 1.5 mg, 3 mg, 6 mg, 6 mg, 6 mg once weekly with acalabrutinib 100 mg BID continuously from Cycle 1 Day 1. Cycles 2+: AZD4573 6 mg once weekly with acalabrutinib 100 mg BID continuously.	5 weeks	Cycle 1 (includes ramp up): Cycle length of 5 weeks Cycle 2 onwards: Cycle length of 3 weeks
Starting dose level **Dose level 1; AZD4573 target dose: 9 mg** Cycle 1, Weeks 1 to 5 (includes ramp up): AZD4573 3 mg, 6 mg, 9 mg, 9 mg, 9 mg once weekly with acalabrutinib 100 mg BID continuously from Cycle 1 Day 1. Cycles 2+: AZD4573 9 mg once weekly with acalabrutinib 100 mg BID continuously.		
Dose level 2; target dose: 12 mg Cycle 1, Weeks 1 to 5 (includes ramp up): AZD4573 6 mg, 9 mg, 12 mg, 12 mg, 12 mg once weekly with acalabrutinib 100 mg BID continuously from Cycle 1 Day 1. Cycles 2+: AZD4573 12 mg once weekly with acalabrutinib 100 mg BID continuously.		

[a] The DLT-assessment period will be extended to incorporate any AZD4573 dosing delay(s), as long as each delay does not exceed 7 consecutive days (± 2 days). Following the delay, the next dose is to be administered at the next regularly scheduled timepoint (± 2 days). To be DLT-evaluable, the participant should have received 3 dose infusions at the target dose level. The DLT-assessment period will end on the original planned day (5 weeks after first dose) or, if there has been a dosing delay, up to ~1 week after the third dose of AZD4573 at the target dose level.

Abbreviations: BID = twice daily; DLT = dose-limiting toxicity.

All participants will begin treatment with an intra-patient ramp up in Cycle 1. In the dose setting cohorts this planned 5-week cycle (including the ramp up) is the DLT-assessment period.

Dose Level 1 (Starting dose level): Once-weekly IV administration of AZD4573 with oral administration of acalabrutinib 100 mg twice daily continuously:

- Week 1: 3 mg AZD4573 once weekly and 100 mg acalabrutinib twice daily
- Week 2: 6 mg AZD4573 once weekly and 100 mg acalabrutinib twice daily
- Week 3: 9 mg AZD4573 once weekly and 100 mg acalabrutinib twice daily
- Week 4: 9 mg AZD4573 once weekly and 100 mg acalabrutinib twice daily
- Week 5: 9 mg AZD4573 once weekly and 100 mg acalabrutinib twice daily

Dose Level 2: Once-weekly IV administration of AZD4573 with oral administration of acalabrutinib 100 mg twice daily continuously.

- Week 1: 6 mg AZD4573 once weekly and 100 mg acalabrutinib twice daily
- Week 2: 9 mg AZD4573 once weekly and 100 mg acalabrutinib twice daily
- Week 3: 12 mg AZD4573 once weekly and 100 mg acalabrutinib twice daily
- Week 4: 12 mg AZD4573 once weekly and 100 mg acalabrutinib twice daily
- Week 5: 12 mg AZD4573 once weekly and 100 mg acalabrutinib twice daily

Dose Level -1: Once-weekly IV administration of AZD4573 with oral administration of acalabrutinib 100 mg twice daily continuously.

- Week 1: 1.5 mg AZD4573 once weekly and 100 mg acalabrutinib twice daily
- Week 2: 3 mg AZD4573 once weekly and 100 mg acalabrutinib twice daily
- Week 3: 6 mg AZD4573 once weekly and 100 mg acalabrutinib twice daily
- Week 4: 6 mg AZD4573 once weekly and 100 mg acalabrutinib twice daily
- Week 5: 6 mg AZD4573 once weekly and 100 mg acalabrutinib twice daily

Upon completion of the 5-week DLT-assessment period, participants will remain on their target dose level of AZD4573 administered intravenously once weekly in combination with daily orally administered acalabrutinib 100 mg twice daily in 3-week treatment cycles until disease progression, an unacceptable drug-related toxicity occurs as defined in the protocol, or the participant withdraws or is withdrawn from the study for other reasons. No further intra-patient dose escalation (other than the ramp up to the assigned target dose level) will be allowed.

After completion of the 5-week DLT-assessment period, dose reduction of AZD4573 with each cycle or within a cycle may be applied, on an individual participant basis, based upon the grade of toxicity experienced by the participant. Dose modification provisions are provided in Section 15.12. All participants who discontinue study treatment (ie, both drugs) will have a SFU visit 30 (± 7) days after the last dose of study drug(s).

All participants will be followed for survival until death, loss to follow-up, AstraZeneca closes the study, or withdrawal of consent, whichever occurs first.

Dose setting cohorts will initially enrol 3 to 6 participants for each new dose level. If a new dose level cohort has fewer than 3 DLT-evaluable participants, non-evaluable participants will be replaced before making an escalation or de-escalation decision unless unacceptable toxicity is observed prior to the enrolment of 3 participants. If 6 participants are initially enrolled, all 6 must have the opportunity to complete the DLT-assessment period before making an escalation or de-escalation decision.

Dosing will be staggered by at least one week between the first and the second participant dosed in each new dose level cohort. Subsequent participants dosed will be staggered by a minimum of 3 days until a decision is made regarding dose escalation or de-escalation.

The dose-escalation decision will follow the decision rules based on the mTPI-2 design (Guo et al 2017) with a 30% (±5% Equivalence Interval Margin) target DLT rate. The decision regarding dose escalation (stay at the current dose, escalate, de-escalate, or de-escalate and never be used again due to unacceptable toxicity) will be determined using the decision rules as discussed in detail in Section 15.2.

Although 3 to 9 participants per dose level may be evaluated to make dose escalation/ de-escalation decisions per mTPI-2, additional participants (up to approximately 21 evaluable per safe dose regimen) may be enrolled in backfilling to collect additional tolerability, PK, and exploratory data.

To assess potential delayed toxicity, an analysis of safety data will be performed and shared with the SRC after completion of the dose setting portion of the study, but prior to moving to dose expansion. This analysis will focus on treatment-emergent AEs beyond the DLT-assessment period and will be taken into account when selecting the RP2D to be taken into the Part B expansion phase.

If emerging data from backfilled participants would result in mTPI-2 directing a dose de-escalation at a previously-cleared dose level, the SRC will review safety data and determine whether the lower dose level of AZD4573 should be selected for further development.

Part B: Expansion (DLBCL subtype cohorts)

After determining the RP2D in Part A (dose setting), separate expansion cohorts for GCB and non-GCB DLBCL subtypes may be opened at the RP2D in Part B.

Participants who start this study in Part B will enter the intra-patient ramp-up period, in which the once-weekly IV dose of AZD4573 is increased over 3 weeks until the RP2D is reached and administered at Weeks 3 to 5. From Cycle 2 onwards, the RP2D is administered once weekly in 3-week cycles. Acalabrutinib (100 mg twice daily) is taken orally continuously from Day 1 of Cycle 1 Week 1.

For primary analyses, a total of approximately 21 RP2D-treated response-evaluable participants of GCB subtype and approximately 21 RP2D-treated response-evaluable participants of non-GCB subtype will be incorporated, including participants from Part A and Part B. The total number of evaluable participants treated in Part B will be up to approximately 42.

The data cut-off for the primary analysis for each expansion subgroup will occur after all participants have had the opportunity to be followed for at least 6 months since their first dose in the expansion subgroup or when 75% of participants have progressed or died in the cohort, whichever occurs first.

Participants will continue to be followed for survival after objective disease progression until death, lost to follow-up, AstraZeneca closes study or withdrawal of consent, whichever occurs first.

Modifications to dose and/or schedule may be made moving forward based on emerging data. Alternate frequencies, schedules, and sequences may be instigated by protocol amendment.

13.2 Scientific Rationale for Study Design

13.2.1 DLBCL Participants

The study design proposed here is based on both preclinical and clinical data from DLBCL tumours which suggests that the underlying biology of the disease is influenced by the cell of origin (reviewed by Nowakowski et al 2019). Tumours of non-GCB subtypes (activated B cells in particular) exhibit significantly enhanced activity of the NF-κB transcription factor family that mediates both B-cell survival and proliferation. As NF-κB is activated by BTK signaling, it has been hypothesised that non-GCB DLBCLs may be particularly sensitive to inhibition of that kinase. In the FTIH study (D8230C0001), single-agent responses have been observed in both GCB and non-GCB subsets of participants; it is therefore important to identify efficacy in both GCB and non-GCB DLBCL subsets. Extensive genotyping of tumour

samples is also included to supplement and take advantage of further evolving information concerning the clinical course of participants with specific abnormalities (eg, “double hit” lymphomas).

Preclinical studies investigating a combination of AZD4573 and acalabrutinib in OCI-LY10 NHL models indicate significantly improved DoR post-completion of dosing as compared to each drug alone and was well tolerated in combination. Additionally, combination of AZD4573 with acalabrutinib also resulted in more durable responses in an ABC DLBCL xenograft model CCI [redacted]

Phase I/II clinical data with the first generation BTK inhibitor ibrutinib have also been regarded as promising, although monotherapy with this drug is insufficient for many r/r DLBCL participants. Overall, responses were observed in 25% (20/80) of participants, including partial responses (PR; n = 12) and complete responses (CR; n = 8). With a median post-treatment follow-up period of 11.53 months, median PFS and overall survival (OS) were 1.64 months and 6.41 months, respectively (Wang et al 2020, Wilson et al 2015).

Given this mechanistic data, combination of a next generation BTK inhibitor (acalabrutinib) with an agent with a non-overlapping mechanism of action (CDK9 inhibition) that exhibits activity in GCB and non-GCB tumour types may prove still more valuable for r/r DLBCL participants.

Acalabrutinib exhibits monotherapy activity in participants with r/r CLL (Awan et al 2019) and has been preliminarily assessed as monotherapy in participants with r/r de novo DLBCL (Dreyling et al 2018, Dyer et al 2018) as well. In the latter study, among 21 participants enrolled, an ORR of 24% (including 19% CRs) was observed.

As is now typical for agents targeting cell death pathways (eg, venetoclax) and based on previous Phase I experience with AZD4573 (see Section 2.2.6), an intra-patient dose ramp up is employed to minimise the probability of TLS.

Given acalabrutinib’s previously demonstrated activity in a range of B-cell malignancies, its relatively well-tolerated side-effect profile, its initial demonstration of clinical activity in the difficult-to-treat population of r/r DLBCL as monotherapy, and mechanism of action (non-overlapping with CDK9 inhibitors), combination therapy may reasonably be expected to yield greater clinical benefit than with either agent alone in a population with significant unmet medical need.

13.2.2 MZL Participants

CCI [redacted]

CCI These findings are similar to those reported in the Phase II open-label study which supported accelerated FDA approval of ibrutinib in participants with MZL: among 60 evaluable with a median of 2 prior treatments (range 1-9), the ORR was 48% (3% CR, 45% PR) (Noy et al 2017).

Given the demonstrated activity of BTK inhibitors in MZL (Lue et al 2020), their relatively well-tolerated safety profile, and a mechanism of action that is non-overlapping with CDK9 inhibitors, it is hypothesised that combination therapy with AZD4573 and acalabrutinib may yield greater clinical benefit than with either agent alone in participants with MZL.

This first module of the protocol is intended to allow preliminary establishment of the safety and efficacy of AZD4573 and acalabrutinib together, potentially allowing sequential introduction of combinations with additional agents in subsequent modules.

13.3 Justification for Dose

The starting dose of AZD4573 selected for this study is 3 mg (Week 1 of Cycle 1) for the initial dose of the intra-patient ramp-up period in the dose setting cohorts. The initial target dose following the ramp up is 9 mg (dose level 1) attained on Week 3 of Cycle 1. During the first cycle, participants will receive a single dose of AZD4573 once weekly beginning with 3 mg Week 1, 6 mg Week 2, and 9 mg for each of Weeks 3 to 5. Participants will also receive acalabrutinib 100 mg twice daily continuously from Day 1 of Cycle 1. Every cycle beyond Cycle 1 will be 3 weeks in length and participants will receive 9 mg infusions of AZD4573 once weekly in combination with acalabrutinib 100 mg twice daily continuously.

The starting and target doses of AZD4573 are selected based on the ongoing Phase I, FTIH study of AZD4573 in haematological tumours (D8230C00001).

The planned intra-patient dose escalation, the cohort escalation scheme, and the dosing schedule have the flexibility to be amended in light of emerging PK, safety, and pharmacodynamic and available efficacy data, which will be reviewed on an ongoing basis throughout the study.

The ongoing Phase I, FTIH study (D8230C00001) of AZD4573 in haematological malignancies, which includes DLBCL, has studied AZD4573 at two dose levels: 18 mg (2 days on/12 days off and/or once weekly) and 12 mg administered once weekly, continuously. At 18 mg, N = 5 participants were evaluable for DLT-assessment, of which 2 had DLTs of clinical TLS and Grade 3 acute kidney injury regarded as secondary to TLS, respectively; all 5 participants in the 18 mg cohort had DLBCL. As a consequence of identifying 2 DLTs among 5 evaluable participants, the SRC agreed to de-escalate dosing from 18 mg to 12 mg weekly and to recruit a further 10 participants in Cohort 2A. No DLTs of

clinical TLS were observed at the 12 mg target dose. At 12 mg, N = 6 participants (4 DLBCL and 2 MM) were evaluable for DLT-assessment. There were 3 events of isolated Grade 4 AST elevations in 2 participants (1 with DLBCL, 1 with MM). These Grade 4 AST elevations met the definition of DLT in versions 2 and 5 of the protocol (dated 7 July 2017 and 18 April 2019), but were transient (less than 4 days duration) and were not accompanied by clinical signs and symptoms of significant hepatic dysfunction. Review of the data (December 2019) by AstraZeneca's Hepatic Safety Knowledge Group and external industry experts concluded that isolated asymptomatic reversible Grade 4 enzyme elevations should not be regarded as DLTs unless prolonged and accompanied by other clinical changes. Study investigators concurred with this interpretation and the protocol was amended accordingly to update the DLT definition. The protocol version including the revised DLT definition has been approved by competent authorities in the United Kingdom, Netherlands, and Germany. Sponsor review of the data CCI [redacted] from participants treated weekly with 12 mg AZD4573 has revealed no instances of DLT under the active CSP v7.0 definition.

The SRC for Study D8230C00001 met CCI [redacted] to review the safety data for Arm A (ie, participants with r/r haematological malignancies excluding AML/ALL/high risk MDS/CMML/CLL and Richter's syndrome), including Cohort 1A (target dose of 18 mg; 2 days on/12 days off and/or once weekly) and Cohort 2A (target dose 12 mg once weekly). The outcome of this meeting was a unanimous vote that the 12-mg once-weekly regimen be declared as a tolerated dose for AZD4573 monotherapy in this setting.

Given the clinical experience outlined above, AstraZeneca believes it is prudent to open Study D8230C00002 with a dosing regimen for AZD4573 (in combination with acalabrutinib) one dose level below the SRC-approved tolerated dose for AZD4573 monotherapy in Arm A of Study D8230C00001; hence, a target dose of AZD4573 9 mg once weekly in combination with 100 mg twice daily acalabrutinib is proposed for inclusion in Study D8230C00002.

The clinical data will be used to refine a PK/PD/efficacy model, and future decisions on dose regimens and escalations will be based on the observed clinical data to date and this refined model.

The acalabrutinib 100 mg twice daily regimen is the recommended regimen for use in adult participants with mantle cell lymphoma (MCL) who have received at least one prior therapy and in adult patients with CLL or SLL (Calquence United States Prescribing Information). Acalabrutinib 100 mg twice daily has been evaluated in various indications (ie, B-cell malignancies and solid tumours) alone and in combination with anti-CD20 antibodies, chemotherapy, a phosphatidylinositol-3-kinase (PI3K) inhibitor, and an anti-programmed cell death 1 (anti-PD-1) antibody. No DLTs have been identified for acalabrutinib alone or when

given in combination with these agents. Therefore, the proposed dosage for this protocol for acalabrutinib is 100 mg twice daily.

13.4 End of Study Definition

Please refer to Section 4.5 for the definition of the end of the study. Module 1 will be considered complete once the last participant enrolled in this Module undergoes a 30-Day Safety Follow-up visit, or if the treating site has confirmed the SFU visit will not be performed. Participants still receiving clinical benefit from AZD4573 and continuing treatment after the data cut-off for the primary analysis will be considered to have completed Module 1 on the date AZD4573 is permanently discontinued.

In addition, the study may be terminated, or individual centres closed at the discretion of AstraZeneca (please refer to Appendix A 9). AstraZeneca may also terminate the module prematurely if concerns for safety arise within this study or in any other study with AZD4573 and/or acalabrutinib.

The data cut-off for the primary analysis for each expansion subgroup will occur approximately 6 months following last participant first dose in the expansion subgroup or when 75% of participants have progressed or died in the cohort, whichever occurs first.

The results from Module 1 will be reported to Regulatory Authorities within one year of the end of module.

14 STUDY POPULATION – MODULE 1

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

Participants must meet the inclusion and exclusion criteria of both the core and module protocol. Where there are differences in stringency or cut-off values, the specific module takes precedence. For example, if haematological medication parameters are stricter in the module than in the core, the Investigator should adhere to the module criteria.

14.1 Inclusion Criteria

Each participant should meet all the inclusion criteria (and none of the exclusion criteria) for this study in order to be assigned to a study cohort. Under no circumstances can there be exceptions to this rule.

NOTE: This Module will be enrolling participants with DLBCL or MZL only.

For inclusion in the study, participants must fulfil all of the following criteria:

1 Participants must meet the eligibility criteria described in Section 5.1.

2 Participants with histologically confirmed, r/r DLBCL or r/r MZL, for whom a clinical study is the best option (in the opinion of the Investigator) for next treatment based on response and/or tolerability to prior lines of therapy.

PART A

- Participants with r/r DLBCL, including subtypes such as DLBCL not otherwise specified [NOS], high-grade B-cell lymphoma [HGBCL], primary mediastinal large B-cell lymphoma [PMBCL], or large B-cell lymphoma transformed from indolent B-cell lymphomas (including but not limited to Richter Syndrome, transformed Follicular Lymphoma, transformed MZL), or r/r MZL:
  - Diagnosis must be confirmed by biopsy and be immunohistologically characterised.
  - For participants with DLBCL, cell of origin subtype shall be characterised locally and tumour tissue must also be available for sending to AstraZeneca for central cell of origin/pathology testing (see below).

    All participants in Part A (dose setting) must consent to and provide archival tumour specimens, preferably in the form of a formalin-fixed paraffin embedded block (tissue derived from the diagnostic tumour or a metastatic site). If this is not possible, an appropriate number of slides of freshly prepared unstained 5-micron sections from the archival tumour block may be provided as defined in the study Laboratory Manual. Archival tumour specimens must be obtained within 24 months before the first dose of IP. If archival material is unavailable or unsuitable for use, participants must consent to and undergo a fresh tumour biopsy during the screening period. A fresh biopsy is strongly encouraged and preferred, however, a participant will be enrolled based on the prior pathology report.

PART B

Participants with r/r de novo DLBCL, GCB or non-GCB subtype:

- Must have received SoC first-line therapy.
- Diagnosis must be confirmed by biopsy and cell of origin subtype characterised locally prior to enrolment and DLBCL be immunohistologically characterised.
- A newly obtained tumour biopsy is strongly encouraged and preferred at Screening to confirm cell of origin status and determine DLBCL subtype. The participant will be enrolled based on a prior pathology report.

  A recent biopsy that was taken as part of SoC prior to screening consent for this study is acceptable if no treatment was administered between the biopsy and the first dose of study treatment, and the biopsy was taken within 60 days prior to receiving the first dose.

If fresh biopsy is not feasible/safe per local interventional radiologist or biopsy attempt fails to retrieve viable lymphoma tissue the participant can still be considered for the study (Part B) after discussion with the Sponsor's medical monitor.

3 Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (according to the Lugano criteria [Cheson et al 2014]).

4 Participants must have failed at least two prior therapies for the treatment of current disease. Participants shall not be eligible for curative treatment options, and have no standard therapy available (including CAR-T cell therapy).

5 Adequate haematologic function at Screening, as defined in Table 9:

(a) No growth factor support within 14 days prior to the date of the screening laboratory assessment.

(b) No transfusions within 7 days prior to the date of the screening laboratory assessment.

Table 9 Criteria for Adequate Haematological Function

Category	Parameter	Value
Haematologic	Haemoglobin	≥ 8.0 g/dL
	Absolute neutrophil count	≥ 1000 cells/mm^3 (1.0 × 10^9/L)
	– Platelet count	≥ 75,000 cells/mm^3 (75 × 10^9/L) without bone marrow involvement
		≥ 50,000 cells/mm^3 (50 × 10^9/L) with bone marrow involvement

– If indicated, transfusions or growth factors can be administered during the screening period, but such cases of deterioration of haematological function must be discussed with the Medical Monitor, to confirm start of study treatment.

6 **Optional** tumour biopsy on study: Participants are also encouraged to consent to and undergo an optional tumour biopsy at disease progression to support correlative biomarker studies.

7 All participants must be willing and able to provide mandatory baseline bone marrow biopsy/aspirate.

14.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1 Participants must comply with the exclusion criteria described in Section 5.2.

2 Current refractory nausea and vomiting, malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach, extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.

3 Prior use of standard anti-lymphoma therapy or radiation therapy within 14 days of receiving the first dose of study treatment.

4 Requires treatment with strong CYP3A inhibitors or inducers (please refer to Appendix F for a list of strong inhibitors and inducers of CYP3A).

5 Requires treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Participants receiving proton-pump inhibitors who switch to H_2-receptor antagonists or antacids are eligible for enrolment to this study (see Section 15.11.4).

6 Serologic status reflecting active hepatitis B or C infection:

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

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

7 Active Cytomegalovirus (CMV) infection (positive CMV immunoglobulin M [IgM] and positive PCR result).

8 Requires or receiving therapeutic anticoagulants, with the exception of short-acting heparins, within 7 days of first dose of study treatment. Novel oral anticoagulants are allowed except for the initial high dose treatment period.

9 Participants on dual antiplatelet and therapeutic anticoagulant therapy (eg, aspirin and therapeutic doses of low molecular weight heparin).

10 Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists.

11 History of or ongoing confirmed progressive multifocal leukoencephalopathy (PML).

14.3 Lifestyle Considerations

Please refer to Section 5.3, in addition to Section 14.3.1.

14.3.1 Meals and Dietary Restrictions – Module 1

Acalabrutinib is best taken with water and can be taken with or without food. As acalabrutinib is metabolised by CYP3A, participants should be strongly cautioned against using herbal remedies or dietary supplements (in particular, St John's wort, which is a potent CYP3A inducer).

Otherwise, participants should maintain their regular diet unless modifications are required to manage an AE such as diarrhoea, nausea, or vomiting.

14.4 Screen Failures

Please refer to Section 5.4.

15 STUDY INTERVENTION – MODULE 1

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

15.1 Study Intervention(s) Administered

15.1.1 Investigational Products

AZD4573 will be administered as an absolute (flat) dose, 2-hour (± 15 minutes) IV infusion once weekly, at least 5 days apart, in combination with orally administered acalabrutinib 100 mg twice daily continuously. For both Part A and Part B of this study, Cycle 1 consists of 5 weeks, with a dose ramp up. Subsequent cycles are 21 days (3 weeks) with once-weekly dosing of AZD4573 in combination with acalabrutinib 100 mg twice daily continuously.

AZD4573 and acalabrutinib will be supplied by AstraZeneca. CCI [redacted] Detailed information on the drug products and administration guidelines are in the AZD4573 Handling Instructions and acalabrutinib participant leaflet.

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines and will be translated into the local language. The labels will fulfil Good Manufacturing Practice Annex 13 requirements for labelling.

All IPs should be kept in a secure place under appropriate storage conditions. The IP label on the vial (AZD4573) or bottle (acalabrutinib) specifies the appropriate storage conditions.

Participants enrolled in this study module will receive acalabrutinib in combination with AZD4573, in accordance with the dosing scheme provided in Section 13.1. Acalabrutinib is intended to be administered orally every day, twice daily with approximately 240 mL of water and can be administered without regard to food. Doses should be administered 12 hours apart (a window of ± 1 hour is allowed) at approximately the same times each day. Treatment with AZD4573 and acalabrutinib, in Part A and Part B, may be continued until disease progression, an unacceptable drug-related toxicity occurs as defined in the protocol, or the participant withdraws or is withdrawn from the study for other reasons. The acalabrutinib capsules should be swallowed intact. Participants should not attempt to open capsules or dissolve in water. If vomiting occurs after taking acalabrutinib, the participant should not retake acalabrutinib until the next scheduled dose.

On the day of PK collection, acalabrutinib capsules should be brought to site by the participant and taken within 5 minutes before initiation of AZD4573. The actual date and time of AZD4573 and acalabrutinib dosing will be recorded.

Table 10 Investigational Products

Intervention Name	AZD4573	Acalabrutinib
Type	Drug	Drug
Dose Formulation	Concentrate for solution for infusion	Capsules
Unit Dose Strength(s)	1.5 mg/mL	100 mg
Dosage Level(s)	1.5 mg – 12.0 mg	100 mg BID
Route of Administration	IV infusion	Oral
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca
Packaging and Labelling	Study Intervention will be provided in vials. Each vial will be labelled as required per country requirement	Study Intervention will be provided in bottles. Each bottle will be labelled as required per country requirement
Current/Former Name(s) or Alias(es)	AZD4573/ AZ13810325	Acalabrutinib/ACP-196/Calquence

Abbreviations: BID = twice daily; IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product.

If an acalabrutinib dose is not taken within the allowed window, it can be taken up to 2 hours after the scheduled time with a return to the normal schedule the same or following day. If it has been > 2 hours, the dose should not be taken, and the participant should take the next dose at the next scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit. If a participant needs to take a dose earlier than scheduled, the participant can take the dose up to 2 hours earlier than the scheduled time except on scheduled site visit days. Participants should make every reasonable effort to take the acalabrutinib on time. Guidance on co-administration of acalabrutinib with agents that affect gastric pH is provided in Section 15.11.

15.2 Starting Dose, Dose-Escalation Scheme, and Stopping Criteria

The starting dose of AZD4573 selected for this study is 3 mg (Week 1 of Cycle 1) for the initial dose of the ramp-up period in the dose setting cohorts. The initial target dose following the ramp up is 9 mg (dose level 1). The starting and target dose were based on clinical data from an ongoing Phase I FTIH study of AZD4573 monotherapy (D8230C00001, see Section 13.3). The initial starting dose of AZD4573 was selected based on the safety information for AZD4573 monotherapy in the ongoing first-in-human study (Study D8230C00001) and is at least one dose level below the RP2D for monotherapy.

A study-specific SRC in accordance with its charter, will be responsible for providing ongoing safety surveillance of the study, with regularly scheduled reviews of safety, PK , and other relevant data (see Section 18.6). This committee will be responsible for making recommendations for dose escalation or dose de-escalation recommendations, including recommendations on opening cohorts for backfill, as well as making recommendations regarding further conduct of the study.

This study includes intra-patient dose escalation (ie, ramp-up dosing) in each cohort to reach the target dose level as a safety precaution. The intra-patient dose-escalation scheme and/or dose schedule for each cohort may be modified based on the safety and PK findings of a previous dose level.

For each new dose level, the initial dose setting cohort will require at least 3 evaluable participants and a maximum of 6. A recommendation about the dose level for each next cohort will be made by the SRC, guided by rules based on the mTPI-2 design (Guo et al 2017) with a 30% target DLT rate (± 5%) for MTD (see Table 11): dose escalation (E), stay (S) at the current dose, de-escalation (D), or de-escalation and current dose is unsafe (DU).

Table 11 Decision Rules Based on mTPI-2 for Dose Escalation

Number of DLTs	Number of DLT-Evaluable Participants Treated at Current Dose Level								
	n = 1	n = 2	n = 3	n = 4	n = 5	n = 6	n = 7	n = 8	n = 9
0	S[a]	S[a]	E	E	E	E	E	E	E
1	S[b]	S[b]	S	S	E	E	E	E	E
2		DU	D	D	D	S	S	S	E
3			DU	DU	D	D	D	D	S
4				DU	DU	DU	D	D	D
5					DU	DU	DU	DU	DU
6						DU	DU	DU	DU

Number of DLTs	Number of DLT-Evaluable Participants Treated at Current Dose Level								
7							DU	DU	DU
8								DU	DU
9									DU

[a] Changed from E to S as a minimum of 3 evaluable participants are needed to make a dose-escalation decision.

[b] Changed from D to S as a minimum of 3 evaluable participants are needed to make a dose de-escalation decision.

Note: E = escalate to the next higher dose level, S = stay at the current dose level, D = de-escalate to the next lower dose level; DU = de-escalate to the previous lower dose and the current dose will never be used again due to unacceptable toxicity.

Abbreviations: D = de-escalation; DLT = dose-limiting toxicity; DU = dose unsafe; E = escalation; mTPI-2 = modified toxicity probability interval; S = stay.

A dose level will be considered as having unacceptable toxicity, with no additional participants enrolled at that dose level and above, if it has an estimated 95% or more probability of exceeding the 30% target DLT rate. Otherwise, dose escalation is terminated when the prespecified maximum target dose is reached (AZD4573 12 mg).

If a stay decision is made, additional participants may be enrolled (usually in cohorts of 2 to 6 participants) up to a maximum of 9 total evaluable participants for a given dose level and a maximum of 24 evaluable participants for dose setting (ie, a maximum of 9 evaluable participants at each of two dose levels and 6 evaluable participants at the third dose level).

At any timepoint during the study, the occurrence of a fatal AE deemed related to study therapy (after full etiological work-up and in discussion with the SRC) will result in accrual stoppage and a comprehensive review of safety. In addition, potential safety signals arising from Grade ≤ 4 treatment-related AEs will be reviewed in the context of the overall benefit/risk. On review any event deemed to adversely affect overall benefit risk will trigger an ad hoc SRC for comprehensive safety review.

In the case of PHL, if bilirubin remains elevated (compared to baseline) at 96 hours (-2/+12 hours) after the start of the infusion, the participant must be discontinued from the study and biochemistry followed until resolution. The Sponsor must be notified immediately.

Part A participants, including backfills, receiving the RP2D of AZD4573 + acalabrutinib combination therapy beyond the Cycle 1 DLT-assessment period and Part B participants receiving AZD4573 + acalabrutinib combination therapy from their first Cycle 1 dose onwards will be monitored for safety using the same DLT criteria employed during dose setting. If, on an ongoing basis, > 30% of participants experience any safety events that meet the criteria of a DLT or > 30% of participants discontinue study treatment due to TLS, enrolment into the expansion cohorts may be paused for evaluation of the study data by the

SRC. Following SRC review additional monitoring may be implemented and/or enrolment and dosing may resume at a lower combination dose level or a modified schedule as defined in the dose setting phase. Further details will be provided in the Medical Monitoring Plan.

15.3 Definition of Dose-limiting Toxicity (DLT)

A Dose Limiting Toxicity is defined as any event that meets the DLT criteria listed in this section, unless unequivocally due to underlying malignancy or an extraneous cause.

Any participants receiving AZD4573 beyond the dose escalation/DLT-assessment period will be monitored for safety using the same DLT criteria used during the DLT-assessment period.

The SRC will make a recommendation to stop or continue recruitment after review of the data from each cohort (see Section 18.6).

The DLT-assessment period applicable in Part A of this module is normally 5 weeks (DLT observation will continue throughout the study for Part A and Part B). Any participant who does not complete the DLT-assessment period in Part A may be replaced, with the exception of a participant who experiences a DLT; these participants will not be replaced.

Additional participants enrolled at a previously-cleared dose level to provide supplemental safety, efficacy, PK, and pharmacodynamics data will not be replaced or evaluated for DLT in support of dose-escalation decisions. However, these additional participants will be included in the determination of MTD/RP2D at the end of the dose-escalation process.

Any AE that meets the DLT criteria in the opinion of the principal Investigator should be reported to the Medical Monitor within 24 hours of knowledge of the event.

A DLT will be defined as the occurrence of any of the following, unless unequivocally due to underlying malignancy or an extraneous cause:

DLT criteria (CTCAE version 5.0):

- Any Grade ≥ 3 non-haematological toxicity except:
  - Grade 3 nausea, vomiting, or diarrhoea despite premedication that respond to medical management (eg, improve by 1 or more severity grade within 72 hours of onset of toxicity, or 96 hours [-2/+12 hours] from the start of dose, whichever is the sooner).
  - Grade ≥ 3 serum lipase and/or amylase that return to initial eligibility criteria within 72 hours of onset of toxicity or 96 hours (-2/+12 hours) post start of dose, whichever is the sooner. Grade ≥ 3 serum lipase and/or amylase that do not return to meet initial eligibility criteria within 72 hours of onset of toxicity or 96 hours (-2/+12 hours) post start of dose, whichever is the sooner, will be considered a DLT.

- A delay in dosing of more than approximately 7 consecutive days (± 2 days), in other words, more than 1 missed dose, due to a dose-related toxicity occurring during the 5-week DLT-assessment period (toxicity that is clearly and directly related to the primary disease or to another aetiology is excluded from this definition).

Isolated elevations of transaminases:

- Grade 3 elevations (≥ 5 × ULN) in ALT or AST, without concomitant elevation in total bilirubin > 2 × ULN, that do not return to Grade 1 within 7 days from start of dosing.
- Grade 4 elevations in ALT (≥ 20 × ULN) of any duration irrespective of total bilirubin.
- Grade 4 elevations in AST (≥ 20 × ULN) without concomitant elevation in ALT ≥ 20 × ULN or total bilirubin ≥ 2 × ULN that do not return to Grade 1 within 7 days from start of dosing.

Elevations in transaminases with concomitant elevation of bilirubin (Potential Hy's Law [PHL]):

- Elevations in ALT or AST ≥ 3 × ULN with concomitant elevation in total bilirubin ≥ 2 × ULN where bilirubin does not return to meet initial eligibility criteria within 72 hours of onset or 96 hours of start of dosing (-2/+12 hours) whichever is the sooner, and/or ALT or AST do not return to meet initial eligibility criteria within 7 days post start of dose.
- Elevations in ALT or AST ≥ 3 × ULN with concomitant elevation in total bilirubin ≥ 2 × ULN and INR > 1.5 × ULN (or > 1.5 × baseline, if elevated at baseline) of any duration.
- Elevations in ALT or AST ≥ 3 × ULN with concomitant elevation in total bilirubin ≥ 2 × ULN of any duration if associated with symptoms or signs of liver impairment (eg, appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%).

Any of the following <u>haematological</u> toxicities:

- CTCAE Grade 4 neutrophil count decrease lasting > 7 days, despite growth factor support.
- Grade ≥ 3 febrile neutropenia (absolute neutrophil count [ANC] < 1.0 ×109/L, fever > 100.9°F [or > 38.3°C]) of any duration despite supportive care.
- CTCAE Grade 4 thrombocytopenia lasting more than 7 days or Grade ≥ 3 thrombocytopenia, of any duration, associated with ≥ Grade 2 bleeding.

- CTCAE Grade 4 anaemia despite transfusion.

Any Tumour Lysis Syndrome meeting the following criteria:

- Grade ≥ 3 clinical TLS (Appendix F) that occurs despite protocol-recommended management will be considered a DLT.
- Laboratory TLS (Appendix F) will be considered a DLT if the metabolic abnormalities do not resolve within 5 days despite protocol-recommended management.

Note: All DLT events of TLS should be graded according to the Howard modification of the Cairo-Bishop criteria as part of TLS monitoring (Section 17.1.5 and Appendix F), while CTCAE grade should be applied on AE/SAE reports.

The definition of DLT excludes:

1 Grade 3 fatigue for ≤ 7 days after onset.

2 Isolated laboratory changes of any grade without clinical sequelae or clinical significance, with the exception of transaminase and bilirubin abnormalities described above.

3 Isolated changes in GGT (ie, with no corresponding elevation in AST, ALT, ALP, Total bilirubin or INR, and no symptoms suggestive of hepatic injury) will not be classified as a DLT.

15.4 Definition of Maximum Tolerated Dose (MTD)

The MTD is defined as the highest dose level associated with the target DLT rate of 30% (± 5%) during the DLT-assessment period.

15.5 Definition of Recommended Phase II Dose (RP2D)

The RP2D is the recommended dose selected in consultation with the SRC based on an assessment of aggregate safety data and all relevant clinical and nonclinical data available at that time. The RP2D for continued clinical development of AZD4573 + acalabrutinib will be assessed as safe and tolerable and will not exceed the MTD.

15.6 Definition of DLT-evaluable Participant

A DLT-evaluable participant is defined as a participant 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 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.

Or

- Has experienced a DLT during the DLT-assessment period.

15.7 Duration of Therapy

Treatment with AZD4573 and acalabrutinib, in Part A and Part B, may be continued until disease progression, an unacceptable drug-related toxicity occurs as defined in the protocol, or the participant withdraws or is withdrawn from the study for other reasons.

For both Part A and Part B, Cycle 1 comprises 5 weeks with a ramp-up period. Cycle lengths are 3 weeks from Cycle 2 onwards. For information on dosing schemes and cycle lengths, see Figure 5 and Table 8.

Any participant who is still on treatment and is receiving clinical benefit from the IP by the end of data collection for the primary analysis will be allowed to continue study treatment. Such participants will continue to be monitored for all SAEs up to 30 days after the last dose of IP. However, the database will be closed following end of data collection, and participants remaining on treatment will only be followed for SAEs (paper report). If a participant is continuing study treatment after the end of data collection, the Investigator should refer to the current IB for treatment guidance and safety surveillance.

15.8 Preparation/Handling/Storage/Accountability of Interventions

Please refer to Section 6.8 for general instructions and instructions specific to AZD4573.

Acalabrutinib drug accountability

Participant reported drug administration for acalabrutinib needs to be done on every AZD4573 dosing day, ideally prior to dosing (± 24 hours) and is also to be done after the last acalabrutinib capsule is taken and the leftover capsules returned to site. Drug accountability for acalabrutinib will occur every two weeks (on an AZD4573 dosing day, ideally prior to dosing [± 24 hours]).

The returned number of acalabrutinib capsules needs to be counted and the participant will be asked whether or not acalabrutinib was taken according to the instructed dosing schedule. Deviations from the instructed schedule should be discussed with the participant and recorded both in the source documents and the eCRF.

Discrepancies between the expected and returned number of capsules should be discussed with the participant and recorded in the source documents.

15.9 Measures to Minimise Bias: Randomisation and Blinding

This is an open-label, non-randomised study (please refer to Section 6.9).

15.10 Study Intervention Compliance

AZD4573

Participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

Acalabrutinib

Acalabrutinib drug accountability will be conducted as described in Section 15.8 and this will be recorded by the site. If the participant made an error or dropped/lost capsules the site will need to check that the participant will have sufficient capsules for the following week. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of acalabrutinib capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

15.11 Concomitant Therapy

The Investigator must be informed as soon as possible about any concomitant medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant therapy(ies), including over-the-counter medications, herbal remedies, vaccines, and supplements, taken during the study will be recorded.

15.11.1 Permitted Concomitant Therapy

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded" as listed in Section 15.11.2. Specifically, participants should receive full supportive care during the study and treatment with antibiotics, anti-emetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

After the start of AZD4573 and acalabrutinib administration, blood and platelet transfusions are allowed as clinically indicated at any time during the study and can be given as per local institutional guidelines. If indicated, transfusions or growth factors can be administered during the screening period, but such cases of deterioration of haematological function must be discussed with the Medical Monitor, to confirm start of study treatment.

Supportive care (eg, recombinant growth factor support) and other medications that are considered necessary for the participant's wellbeing, (eg, bisphosphonates), may be given at the discretion of the Investigator and in accordance with local institutional guidelines.

Concomitant use of paracetamol is permitted but is limited to a maximum dose of 4 grams per day.

AstraZeneca recommends administering non-live inactivated vaccines 72 hours prior to administration of the first dose of any IP to avoid biases in the interpretation of safety data due to the potential overlap of vaccine-related AEs with IP AEs.

Permitted concomitant therapy for the management of safety concerns for AZD4573 and acalabrutinib (including TLS) is specified in Section 17.1.10. For participants considered at risk for TLS (see Section 17.1.10.10), administer appropriate hydration and allopurinol or rasburicase per institutional standards before initiating treatment.

15.11.2 Prohibited Concomitant Therapy

Participants must be instructed not to take any medications, including over-the-counter products, herbal remedies, and supplements without first consulting with the Investigator.

The following medications are considered exclusionary during the study. AstraZeneca must be notified if a participant receives any of these during the study:

- Any investigational anti-cancer therapy.
- Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of

hormones for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable.

- Participants may use topical or inhaled corticosteroids as therapy for comorbid conditions. Ongoing use of low-dose systemic corticosteroids (≤ 10 mg/day prednisolone or equivalent is permitted (Section 6.11).
- Warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) are prohibited for all participants in the study. Participants who require anticoagulation prophylaxis before study treatment start or therapeutic anticoagulation for thrombosis while on study will be allowed to receive anticoagulation with a non-vitamin K inhibitor class of anticoagulants. Should participants require either a vitamin K antagonist or combined administration of antiplatelet and therapeutic anticoagulation while on study, acalabrutinib treatment must be discontinued.

For further restrictions on the concomitant use of therapies and possible drug-drug interactions with AZD4573 and acalabrutinib, please refer to Section 6.11 and Section 15.11.4, respectively.

15.11.3 AZD4573 and Concomitant Therapy

For further specific information on AZD4573 and concomitant therapy, please refer to Section 6.11.

15.11.4 Acalabrutinib and Concomitant Treatments

The effect of agents that reduce gastric acidity (antacids or proton-pump inhibitors) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this study indicate that participants should avoid the use of calcium carbonate containing drugs or supplements for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib. Use of omeprazole, esomeprazole, lansoprazole, or any other proton-pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study treatment exposure. However, the decision to treat with proton-pump inhibitors during the study is at the Investigator's discretion, with an understanding of the potential benefit to the participant's gastrointestinal condition and a potential risk of decreased exposure to acalabrutinib. Although the effect of H_2-receptor antagonists (such as famotidine or ranitidine) on acalabrutinib absorption has not been evaluated, if treatment with an H_2-receptor antagonist is required, the H_2-receptor antagonist should be taken approximately 10 hours before or 2 hours after acalabrutinib.

Acalabrutinib is not a strong direct inhibitor or inducer of CYP isoforms; thus, acalabrutinib, at the currently used clinical doses, is unlikely to be a perpetrator of a drug-drug interaction at the level of inhibition or induction of CYP isoforms. The concomitant use of strong

inhibitors/inducers of CYP3A should be avoided (please refer to Appendix F). Because acalabrutinib is metabolised by CYP3A, participants should be strongly cautioned against consumption of grapefruit, grapefruit juice, or Seville orange juice (which contain potent CYP3A inhibitors) or using herbal remedies or dietary supplements (in particular, St. John's wort, which is a potent CYP3A inducer). If a participant requires short-term treatment with a strong CYP3A inhibitor (such as anti-infectives for up to 7 days), interrupt acalabrutinib treatment. From Cycle 2 onwards, if a participant requires a moderate CYP3A inhibitor while on study, decrease acalabrutinib dose to 100 mg once daily. Avoid co-administration of strong CYP3A inducers. If a participant requires treatment with a strong CYP3A inducer, increase the acalabrutinib dose to 200 mg twice daily during concomitant administration with the strong CYP3A inducer and return to recommended dose of 100 mg twice daily after stopping the strong CYP3A inducer.

Concomitant use of paracetamol is permitted but is limited to a maximum dose of 4 grams per day. For participants dosed with AZD4573 and acalabrutinib non-steroidal anti-inflammatory agents such as ibuprofen should also be avoided.

15.12 Dose Modification

Table 12 provides dose reductions options for acalabrutinib.

Table 12 Acalabrutinib Dose Reduction Options

Starting dose	1st dose reduction[a]	2nd dose reduction
100 mg twice daily	100 mg once daily	Discontinue

[a] When reducing to 100 mg acalabrutinib once daily, the morning dose should be retained. If considering dose reduction, please discuss with the Medical Monitor.

Note: Temporary withholding of acalabrutinib for as little as 7 days can cause a transient worsening of disease in DLBCL and/or of constitutional symptoms. Transient worsening of disease during temporary interruption of acalabrutinib (eg, for drug-related toxicity, surgery, or intercurrent illness) may not indicate disease progression. In such circumstances, and if medically appropriate, following discussion with the Medical Monitor, participants may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be done to document whether tumour control can be maintained or whether actual disease progression has occurred.

If the dose of acalabrutinib is reduced for apparent treatment-related AE/SAE, the dose of acalabrutinib should not be re-escalated unless the participant tolerates the reduced dose for greater than 4 weeks and at the Investigator's discretion and in consultation with the Medical Monitor. Such re-escalation may be particularly warranted if further evaluation reveals that the

AE/SAE that led to the dose reduction was not treatment-related. Any changes to the dosing regimen must be recorded on the appropriate eCRF.

Acalabrutinib dose reduction options are described in Table 12 and dose modification and discontinuation guidelines for haematological and non-haematological toxicities (excluding abnormal liver chemistry results) are shown below in Table 13. Dose modifications for AZD4573 and acalabrutinib for abnormal liver chemistry results are described in Table 14.

In general, if a participant experiences a Grade 1 or Grade 2 haematological or non-haematological toxicity, no dose modification is required. If a participant experiences a Grade 3 or Grade 4 toxicity, not attributable to the disease or disease-related processes under investigation, dosing might be interrupted and/or the dose reduced (see Table 12 for acalabrutinib reduction options and Table 13 for recommended dose modifications for AZD4573 and acalabrutinib) and supportive therapy administered as required. If the toxicity resolves or reverts to CTCAE Grade ≤ 2 within 21 days and the participant was showing clinical benefit, treatment with study treatment(s) may be restarted.

If the toxicity does not resolve to CTCAE Grade ≤ 2 within 21 days, then the participant should be withdrawn from the study and observed until resolution of the toxicity. Maximal drug interruption allowed for related toxicity for both AZD4573 and acalabrutinib is ≤ 21 consecutive days.

Table 13 Recommended Dose Modifications for AZD4573 and Acalabrutinib

Event[a]	Occurrence	Action with AZD4573	Action with Acalabrutinib
Tumour Lysis Syndrome (TLS) – Howard Modification of Cairo-Bishop Criteria			
Changes in uric acid, potassium, phosphorus, creatinine or calcium, or symptoms suggestive of clinically significant TLS, in the Investigator's judgement	Any	For any abnormal changes present before dosing, initiate supportive therapy and hold drug for up to 7 days. If not resolved, reduce by 1 dose level.	Withhold acalabrutinib until resolved, resume dosing at the same dose level upon resolution.
		For events of Grade 1 or 2 TLS, resume at same dose level upon resolution.	For events of Grade 1 or 2 TLS, resume at same dose level upon resolution.
		For **1st occurrence** of Grade 3 TLS resume at the same dose upon resolution to Grade 1.	For **1st occurrence** of Grade 3 TLS resume at the same dose upon resolution.

Table 13 Recommended Dose Modifications for AZD4573 and Acalabrutinib

Event[a]	Occurrence	Action with AZD4573	Action with Acalabrutinib
		For **2nd occurrence** of Grade 3 TLS, after resolution to Grade 1, reduce dose by one dose level when restarting AZD4573 except events that in the opinion of the Investigator, in consultation with the Medical Monitor, are not dose-limiting. For **subsequent occurrences** of Grade 3 TLS, further rechallenge and dose level to be discussed with the Medical Monitor. For events of Grade 4 TLS, discontinue AZD4573.	For **2nd occurrence** of Grade 3 TLS, after resolution to Grade 1, reduce dose by one dose level when restarting or discontinue acalabrutinib except events that in the opinion of the Investigator, in consultation with the Medical Monitor, are not dose-limiting. For **subsequent occurrences** of Grade 3 TLS, further rechallenge and dose level to be discussed with the Medical Monitor. For events of Grade 4 TLS, discontinue acalabrutinib.

Table 13 Recommended Dose Modifications for AZD4573 and Acalabrutinib

Event[a]	Occurrence	Action with AZD4573	Action with Acalabrutinib
Non-haematological toxicities (except liver dysfunction)			
Grade 3 or 4 non-haematological toxicities	1st occurrence	Withhold dosing with AZD4573 until the toxicity has resolved to Grade 1, but no longer than 21 days[b]. Adequate supportive therapy as per institutional guidelines should be given. AZD4573 therapy may be resumed at the same dose. No dose modification is required.	Withhold acalabrutinib until recovery to Grade ≤ 2. Restart acalabrutinib at the same dose level.
	2nd and subsequent occurrences	Withhold dosing AZD4573 up to 21 days[b]. Adequate supportive therapy as per institutional guidelines should be given. After resolution to Grade 1, reduce dose by one dose level when restarting AZD4573. If no resolution within 21 days discontinue AZD4573[b]. In case of **subsequent occurrences**, dosing may be modified to skip weekly dose(s) (eg, 2 weeks on/1 week off or to 1 week on/1 to 2 weeks off), after discussing with the Medical Monitor.	Withhold acalabrutinib until recovery to Grade ≤ 2. Restart acalabrutinib with 1 level dose reduction or discontinue (see Table 12).

Table 13 Recommended Dose Modifications for AZD4573 and Acalabrutinib

Event[a]	Occurrence	Action with AZD4573	Action with Acalabrutinib
Haematological Toxicities			
Grade 3 or 4 neutropenia without fever or infection, lasting > 7 days despite growth factor support	1st occurrence	Withhold dosing AZD4573 until Grade ≤ 2 or baseline level. Restart at same dose level following resolution.	Withhold acalabrutinib if Grade 4 neutropenia lasting > 7 days until resolution to Grade ≤ 2 or baseline level and then restart at same dose for **1st occurrence**.
	2nd and subsequent occurrence	Withhold dosing AZD4573 until Grade ≤ 2 or baseline level. Restart with one dose level reduction following resolution. In case of **subsequent occurrences**, dosing may be modified to skip weekly dose(s) (eg, 2 weeks on/1 week off or to 1 week on/1 to 2 weeks off), after discussing with the Medical Monitor.	Withhold acalabrutinib if Grade 4 neutropenia lasting > 7 days until resolution to Grade ≤ 2 or baseline level and then restart at a reduced dose or discontinue (see Table 12).

Table 13 Recommended Dose Modifications for AZD4573 and Acalabrutinib

Event[a]	Occurrence	Action with AZD4573	Action with Acalabrutinib
Grade 3 or 4 neutropenia with infection or fever	1st occurrence	Withhold dosing AZD4573. To reduce the infection risks associated with neutropenia, G-CSF may be administered with AZD4573 if clinically indicated/required as per Institutional practice. Consider secondary prophylaxis with G-CSF as per ASCO/ESMO guidelines. Once the toxicity has resolved to ≤ Grade 2 or to baseline level, AZD4573 therapy may be resumed at the same dose.	Withhold acalabrutinib until infection is resolved, antibiotics no longer required and ANC Grade ≤ 2 or baseline level. Following resolution, resume acalabrutinib with 1 level dose reduction or discontinue (see Table 12).
	2nd occurrence	Withhold dosing AZD4573. Consider using G-CSF as clinically indicated/as per Institutional practice. Follow dose reduction guidelines when resuming treatment with AZD4573 after resolution. Reduce dose by one dose level.	Withhold acalabrutinib until infection is resolved, antibiotics no longer required and ANC Grade ≤ 2 or baseline level. Following resolution, resume acalabrutinib with 1 level dose reduction or discontinue (see Table 12).
	3rd occurrence	Discontinue AZD4573.	Discontinue acalabrutinib.
Grade 3 thrombocytopenia without bleeding	Any	Withhold AZD4573 until Grade ≤ 2 or baseline level. Restart AZD4573 at the same dose level. Continued dosing can be considered at the discretion of the investigator after discussion with the medical monitor.	No action.
Grade 4 thrombocytopenia without bleeding requiring blood or platelet transfusion	1st occurrence	Withhold AZD4573 until Grade ≤ 2 or baseline level. Restart AZD4573 at the same dose level.	Withhold acalabrutinib until Grade ≤ 2 or baseline level. Restart acalabrutinib at the same dose level.

Table 13 Recommended Dose Modifications for AZD4573 and Acalabrutinib

Event[a]	Occurrence	Action with AZD4573	Action with Acalabrutinib
	2nd occurrence	Withhold AZD4573 until Grade ≤ 2 or baseline level. Restart AZD4573 with 1 level dose reduction. If not recovered to Grade ≤ 2 or baseline level discontinue.	Withhold acalabrutinib until Grade ≤ 2 or baseline level. Restart acalabrutinib with 1 level dose reduction or discontinue (see Table 12).
	3rd occurrence	Discontinue AZD4573.	Discontinue acalabrutinib.
Grade 3 or 4 thrombocytopenia with bleeding requiring blood or platelet transfusion	1st occurrence	Withhold AZD4573 until Grade ≤ 2 or baseline level. Restart AZD4573 with 1 level dose reduction. If not recovered to Grade ≤ 2 or baseline level discontinue.	Withhold acalabrutinib until Grade ≤ 2 or baseline level. Restart acalabrutinib with 1 level dose reduction or discontinue (see Table 12).
	2nd occurrence	Discontinue AZD4573.	Discontinue acalabrutinib.

[a] Adverse reactions are graded using National Cancer Institute CTCAE version 5.0. All grades refer to CTCAE grading except for TLS, which uses the Howard modification of Cairo-Bishop criteria (Howard et al 2011).

[b] In cases where more than 21 days are needed, a decision to continue, modify, or discontinue study treatment will be made on a case-by-case basis in consultation with the principal Investigator and the Medical Monitor.

Abbreviations: ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; CTCAE = Common Terminology Criteria for Adverse Events; ESMO = European Society for Medical Oncology; G-CSF = granulocyte-colony-stimulating factor; TLS = tumour lysis syndrome.

Dose modifications for AZD4573 and acalabrutinib for abnormal liver chemistry results are described in Table 14.

Table 14 Recommended Dose Modifications for AZD4573 and Acalabrutinib for Abnormal Liver Chemistry Results

Event[a]	Action	
	AZD4573	Acalabrutinib
Isolated[b] elevations in ALT, AST, or bilirubin		
Grade 1 Isolated ALT/AST ≤ 3 × ULN or Isolated Bilirubin ≤ 1.5 × ULN	Maintain current dose level. Monitor ALT, AST, ALP, and bilirubin at least 1x per week.	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per week.

Event[a]	Action	
	AZD4573	**Acalabrutinib**
Grade 2 Isolated ALT/AST > 3 to ≤ 5 × ULN or Isolated Bilirubin > 1.5-≤ 3 × ULN	After 7 days if hepatic enzymes resolve to Grade ≤ 1, rechallenge at same dose level.	Withhold or continue acalabrutinib (at Investigator discretion, after discussion with the Medical Monitor). To prevent disease progression, monitor disease parameters closely. Monitor ALT, AST, ALP, and bilirubin at least 1x per week. After 7 days if hepatic enzymes appear to be improving and acalabrutinib was withheld, restart acalabrutinib at current dose level.
Grade 3 Isolated ALT/AST > 5-20 × ULN	If recovered to Grade ≤ 1 within 7 days, allow rechallenge at same dose level. If not recovered to baseline level within 7 days, discontinue AZD4573.	Withhold or continue acalabrutinib (at Investigator discretion, after discussion with the Medical Monitor). To prevent disease progression, monitor disease parameters closely. Monitor ALT, AST, ALP, and bilirubin at least 1x per week. After 7 days if hepatic enzymes appear to be improving and acalabrutinib was withheld, restart acalabrutinib with 1 level dose reduction or discontinue.
Grade 3 Isolated Bilirubin > 3-10 × ULN	If recovered to baseline level within 96 hours (-2/+12 hours) of the start of the infusion allow rechallenge at same dose level. If not, discontinue AZD4573	
Grade 4[c] Isolated ALT > 20 × ULN or Isolated Bilirubin > 10 × ULN	Discontinue AZD4573.	Discontinue acalabrutinib.
Grade 4 Isolated elevation (≥ 20 × ULN) in AST without concomitant elevation in ALT ≥ 20 × ULN or concomitant elevation in TBL ≥ 2 × ULN that fails to return to baseline level within 7 days from start of dosing	Discontinue AZD4573.	Discontinue acalabrutinib.

Event[a]	Action	
	AZD4573	**Acalabrutinib**
Grade 4[c] Isolated AST elevation ≥ 20 × ULN without concomitant elevation in ALT ≥ 20 × ULN or TBL ≥ 2 × ULN	**1st occurrence** If recovered to Grade ≤ 1 or baseline level within 7 days of the start of the infusion allow rechallenge at same dose level	Withhold or continue acalabrutinib (at Investigator discretion, after discussion with the Medical Monitor). To prevent disease progression, monitor disease parameters closely. Monitor ALT, AST, ALP, and bilirubin at least 1x per week. After 7 days if hepatic enzymes appear to be improving and acalabrutinib was withheld, restart acalabrutinib at current dose level at the **1st occurrence** and with 1 level dose reduction at the **2nd occurrence**. Discontinue acalabrutinib at the **3rd occurrence**.
	2nd occurrence If recovered to Grade ≤ 1 or baseline level within 7 days of the start of the infusion allow rechallenge with 1 dose level reduction	
	3rd occurrence Discontinue AZD4573	
Concurrent elevations in ALT, AST, or bilirubin (Please also refer to Appendix E for actions to be taken in the event of PHL)		
ALT or AST ≥ 3 × ULN with TBL ≥ 2 × ULN (Potential Hy's Law) **AND** INR ≥ 1.5 × ULN (or ≥ 1.5 × baseline if elevated at baseline) of any duration	Discontinue AZD4573.	Discontinue acalabrutinib.
ALT or AST ≥ 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%	Discontinue AZD4573.	Discontinue acalabrutinib.
ALT or AST ≥ 3 × ULN and TBL ≥ 2 × ULN where TBL does not return to baseline level within 96 hours (-2/+12 hours) from start of dose and/or AST or ALT do not return to baseline level within 7 days from start of dose	Discontinue AZD4573.	Discontinue acalabrutinib.

Event[a]	Action	
	AZD4573	**Acalabrutinib**
Grade 3 elevation (≥ 5 × ULN) in ALT or AST with TBL elevation above baseline level or ULN, but < 2 × ULN that do not return to baseline level within 7 days	Discontinue AZD4573.	Discontinue acalabrutinib.
ALT and AST ≥ 3 × ULN with concomitant TBL ≥ 2 × ULN, NO increase in INR ≥ 1.5 × ULN (or 1.5 × baseline), and NO fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%	If recovered to Grade ≤ 1 or baseline level within 96 (-2/+12) hours, rechallenge at same dose level[c]	Withhold acalabrutinib until recovered. Once recovered, restart acalabrutinib at same dose.

[a] Adverse reactions are graded using National Cancer Institute CTCAE version 5.0. All grades refer to CTCAE grading except for TLS, which uses the Howard modification of Cairo-Bishop criteria (Howard et al 2011).

[b] Elevations in ALT or AST are considered isolated if bilirubin remains below Grade 1, and elevations in bilirubin are considered isolated if ALT and AST remain below Grade 1.

[c] Participants who are considered for rechallenge in the event of Grade 4 transaminase increases or PHL must discuss possible risk of hepatotoxicity with the treating physician, who will document this discussion and participant agreement for continued treatment in the medical records.

Note: Adequate supportive therapy as per institutional guidelines should be given for all toxicities.
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; INR = international normalised ratio; PHL = Potential Hy's Law; TBL = total bilirubin; ULN = upper limit of normal.

15.12.1 Retreatment Criteria

Retreatment is defined as the first dose of study drug after a significant period of intentional pause in study drug treatment (other than missed doses, eg, study treatment put on hold until resolution of COVID-19).

Retreatment criteria (criteria to be met before participant restarts study drug infusions [and capsules, as applicable]):

All participants:

1 Participant has recovered from all treatment-related non-haematological toxicity to CTCAE Grade ≤ 2.

2 Recovery of neutrophils ≥ 1000/µL and platelets ≥ 50,000/µL.

3 Participant has recovered from all hepatic toxicity events within the timeframes described in Table 14 above. If biochemical changes in transaminase(s) and total bilirubin are consistent with the definition of HL, the participant may continue to receive study drug

only if all abnormalities have resolved within the timeframes specified in Table 14 above, there are no symptoms of liver injury and INR has not increased above 1.5 × ULN (or 1.5 × baseline). In these circumstances the participant must be made aware of the unknown potential for liver damage with continued exposure to AZD4573 prior to retreatment. Documentation of continued consent is required.

4 Recovery of uric acid to < ULN.

5 Recovery of changes in uric acid, potassium, phosphorus, creatinine or calcium, or symptoms suggestive of TLS as defined in Table 13.

6 In case of any new deterioration in laboratory values, not fulfilling eligibility criteria and deeded as clinically significant by the Investigator, the Medical Monitor must be contacted to discuss whether AZD4573 dosing can be continued.

15.13 Intervention After the End of the Study

No intervention is planned after the end of the study. However, provisions will be in place for patients still enrolled at the end of the trial to continue to receive study intervention if, in the opinion of the Investigator, they are continuing to receive benefit from treatment.

16 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL – MODULE 1

16.1 Discontinuation of Study Intervention

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Please refer to Section 7.1 for information on discontinuation of study intervention.

16.1.1 Temporary Discontinuation

Refer to Section 15.12 for information on temporary discontinuation and restarting of study intervention.

16.1.2 Rechallenge

Refer to Section 15.12 for information on rechallenge with study intervention.

16.2 Participant Withdrawal from the Study

Please refer to Section 7.2 for information on participant withdrawal from the study.

16.3 Procedures for Handling Participants Incorrectly Initiated on AZD4573 or Combination Therapy

Please refer to Section 7.3 for information on procedures for handling participants incorrectly initiated on AZD4573 or combination therapy.

16.4 Lost to Follow-up

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

Please refer to Section 7.4 for actions to be taken if a participant fails to return to the clinic for a required study visit.

For handling of discontinuation of specific sites or of the study as a whole please refer to Appendix A 9.

17 STUDY ASSESSMENTS AND PROCEDURES – MODULE 1

- Study procedures and their timing are summarised in the SoA (Section 10.2). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The amount of blood collected from each participant for the scheduled assessments, is not anticipated to exceed 440 mL in Cycle 1 (cycle duration 5 weeks), 135 mL in Cycle 2 (cycle duration 3 weeks) and 80 mL in each subsequent cycle (cycle duration 3 weeks). If a participant experiences TLS, maximum 30 mL extra blood will be collected per cycle (5 weeks) for safety reasons. CCI [redacted] Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

17.1 Safety Assessments

17.1.1 Enrolment and Screening

Each potential participant approved for screening is assigned a unique participant enrolment number. If a participant withdraws from the study, then the enrolment number cannot be reused.

Demographic data and other characteristics will be recorded and will include date of birth, race and ethnicity, and alcohol use.

A standard medical, medication and surgical history will be obtained with review of the selection criteria with the participant. Concurrent medical signs and symptoms must be documented to establish baseline severities. Previous and concomitant treatments (coded

according to the World Health Organization Drug Dictionary [WHODRUG]) will be collected for each participant. A disease history, including the date of initial diagnosis, staging within 30 days of first dose of AZD4573, prognostic indices/disease profiling for DLBCL (derived from local laboratory results) and list of all prior anti-cancer treatments, and responses and DoR to these treatments, will also be recorded.

Each participant will undergo screening (see Section 10.2) during the 30 days before admission to confirm eligibility (see Sections 14.1 and 14.2).

17.1.2 Physical Examinations

A complete physical examination, including a standard neurological examination should be completed at Screening and will include, at a minimum: the general appearance of the participant, height, weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Investigators should pay special attention to clinical signs related to previous serious illnesses and new or worsening abnormalities may qualify as AEs.

Symptom-directed physical exams are done thereafter at the visits indicated in the SoA, including the SFU visit (Section 10.2).

17.1.3 Vital Signs

Vital signs will be performed at timepoints specified in the SoA (Section 10.2)

Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

Pulse rate and blood pressure

Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 10 minutes of rest for the participant in a quiet setting.

Pulse rate and blood pressure measurement timepoints are:

- Screening
- Cycle 1 (Weeks 1 to 3) :
  - Predose (up to 2 hours prior to infusion)

  - 1 hour after the start of the infusion (± 10 mins)
  - At the end of the infusion (up to 10 minutes post dose)
  - 4 hours after the start of the infusion (± 30 minutes)
  - 6 hours after the start of the infusion (± 30 minutes)
- From Cycle 1, Week 4 onwards:
  - Predose (up to 30 minutes prior to infusion)
  - At the end of the infusion (up to 30 minutes post dose) on each dosing day
- 30-Day SFU

Body temperature

Body temperature will be measured in degrees Celsius at the following timepoints:

- Predose (up to 2 hours prior to all infusions)

Weight

Weight will be measured in kilograms at the following times:

- Screening,
- Cycle 1 (Weeks 1-3) (predose)
- Cycle 1 Week 4 onwards, of each cycle predose
- 30-Day SFU

17.1.4 WHO/ECOG Performance Status

ECOG performance status will be assessed at the following times (see Section 10.2):

- Screening
- Cycle 1 through Cycle 8:
  - Predose each dose of AZD4573
- Cycles 9+, Day 1 of each cycle:
  - Predose each dose of AZD4573
- 30-day SFU

Performance status should be measured using the ECOG Performance Status Scale (Table 15). It is recommended, where possible, that a participant's performance status be assessed by the same person throughout the study.

Table 15 ECOG Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
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 all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

17.1.5 B Symptoms

Information on B symptoms (eg, unintentional weight loss, fevers, and night sweats) will be collected at the following times (Section 10.2).

- Screening
- Cycle 1 through Cycle 8:
  - Predose AZD4573
- Cycle 9+, Day 1 of each cycle:
  - Predose AZD4573
- 30-day SFU

17.1.6 Clinical Safety Laboratory Assessments

For all participants, results of safety laboratory testing (haematology and clinical chemistry at a minimum) must be available within 72 hours prior to dosing and must be reviewed by the Investigator prior to administration of AZD4573 (all cohorts). If clinically indicated, additional clinical laboratory tests and evaluations may be performed by the Investigator (eg, additional haematology/clinical chemistry panels, TLS parameters, liver enzyme tests); these need to be entered into the eCRF.

This study will use local laboratories.

The following laboratory variables will be measured:

Haematology: complete blood count (CBC) with automated and/or manual differential including, but not limited to, white blood cell count, haemoglobin, haematocrit, platelet count, ANC, and absolute lymphocyte count (ALC), and blast cells. Haematology should be evaluated before dosing while participants are receiving treatment.

Haematology samples will be collected at the following timepoints:

- Screening
- Cycles 1, 2, and 3
  - Predose AZD4573 (within 72h prior to infusion)
  - 24 hours after the start of the infusion
- Cycles 4+
  - Predose AZD4573 (within 72 hours prior to infusion)
  - If clinically indicated, 24 hours after the start of the infusion
- 30-Day SFU

The Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF.

Haematology tests do not need to be repeated before first dose if the first-dose visit is within 3 days of the Screening sample.

Clinical Chemistry: albumin, chloride, bicarbonate, calcium total, magnesium, phosphorous, glucose (fasting preferred), CK, ALP, ALT, ammonia (where available at local institution; to be tested every 2 weeks), AST, urea, , cholesterol, C-reactive protein, creatinine, Factor V (where available at local institution), GGT, lactate dehydrogenase (LDH), phosphate, potassium, sodium, triglycerides, total bilirubin, direct and indirect bilirubin, total protein, uric acid.

Clinical chemistry samples will be collected at the following timepoints:

- Screening
- Cycles 1, 2, and 3
  - Predose AZD4573 (within 72 hours prior to infusion)
  - 24 hours after the start of the infusion
- Cycles 4+

  - Predose AZD4573 (within 72 hours prior to infusion)
  - If clinically indicated, 24-hour after the start of the infusion
- 30-Day SFU

The Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF.

Clinical chemistry and haematology tests do not need to be repeated before first dose if the first-dose visit is within 3 days of the Screening sample.

In addition, GLDH and CPK will be measured at Screening for all participants. If GLDH cannot be performed locally, LDH will be analysed locally and a serum sample must be collected for central retrospective GLDH analysis, which will be performed as applicable. Refer to the Laboratory Manual for details.

Coagulation testing includes aPTT (partial thromboplastin time)/PT (prothrombin time), INR, D-dimer (where available at institution), and fibrinogen.

Samples for coagulation testing will be collected at the following timepoints:

- Screening
- Cycles 1, 2, and 3
  - Predose AZD4573 (within 72 hours prior to infusion)
  - 24 hours after the start of the infusion
- Cycles 4 through 8
  - Predose AZD4573 (within 72 hours prior to infusion)
  - If clinically indicated, 24-hour after the start of the infusion
- Cycles 9+ on Day 1 of each cycle
  - Predose AZD4573 (within 72 hours prior to infusion)
- 30-Day SFU

The Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF.

Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Urine samples should be collected at the following timepoints:

- Screening

- Cycles 1 through 8
  - Predose AZD4573 (within 72 hours prior to infusion)
  - Within approximately 2 hours after the end of the infusion
- Cycles 9+ on Day 1 of each Cycle
  - Predose AZD4573 (within approximately 72 hours prior to infusion)
  - Within approximately 2 hours after the end of the infusion
- 30-Day SFU

Cardiac troponin I or troponin T measurements are required at the timepoints below. Either a troponin I or troponin T assay can be used per SoC at the respective hospital. If the hospital has both a SoC troponin I and troponin T assay available, the investigator should use only one consistently for the duration of the study.

- Screening
- Cycle 1, Weeks 1 through 5
  - Predose (within 72 hours prior to infusion)
  - 24 hours post start of the infusion
- Cycles 2+ on Day 1 of each cycle
  - Predose (within 72 hours prior to infusion)
- 30-Day SFU

Electrolyte panel: calcium, magnesium, potassium.

If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, potassium), and troponin must be done to coincide with the ECG testing.

Supra-renal glands: T4, cortisol, adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH) should be measured at the following timepoints:

- Screening
- Cycle 2 Day 1
  - Predose AZD4573 (within 72 hours prior to infusion)
- 30-Day SFU

Pancreas: Lipase and amylase measurements are required at the following timepoints:

- Screening
- Cycles 1 through Cycle 8
  - Predose AZD4573 (within 72 hours prior to infusion)
- Cycles 9+ on Day 1 of each Cycle
  - Predose AZD4573 (within 72 hours prior to infusion)
- 30-Day SFU

Lipase/amylase tests do not need to be repeated before first dose if the first-dose visit is within 3 days of the Screening sample.

TLS monitoring will include: potassium, calcium, phosphate, uric acid, and creatinine.

TLS monitoring will be performed at the following timepoints:

- Cycle 1, Weeks 1 through 3
  - Predose AZD4573
  - 6 hours (± 30 minutes) after the start of the infusion
  - 24 hours (± 1 hour) after the start of the infusion (and prior to acalabrutinib dosing)

Participants showing signs of clinical or laboratory TLS at 6 hours after the start of the infusion must be admitted for in-patient TLS monitoring for a minimum of 24 hours after the start of the infusion and monitored every 4 to 6 hours during this time (or more frequently if clinically indicated).

For each TLS monitoring timepoint, a TLS Monitoring page in the eCRF is to be filled out.

Hepatitis serology will be conducted at Screening. Hepatitis serology must include hepatitis B surface antigen (HbsAg), hepatitis B surface antibody (anti-HBs), anti-HBc, and hepatitis C (HCV) antibody. Participants who are anti-HBc positive, or have a known history of hepatitis B virus (HBV) infection, should be monitored every 3 months with a quantitative PCR test for HBV DNA (Section 17.1.10.4). In addition, any participants testing positive for any hepatitis serology must have PCR testing for verification purposes.

Pregnancy: a sample for a pregnancy test will be collected from all female participants of childbearing potential at:

- Screening (serum)
- Cycle 1, Week 1

  - Predose
- Cycles 2+ once every 21 days (± 7 days) prior to initiating a new cycle
- 30-day SFU visit

Pregnancy tests after Screening may be serum or urine. Urine β-hCG and quantitative serum β-hCG tests are permitted. If a urine β-hCG test is positive or indeterminate, quantitative serum β-hCG will be performed for confirmation. Additional testing may be performed at Investigator discretion, for example in the event of suspected contraception failure.

Liver chemistry tests: **For any participant on study who experiences elevated ALT /AST ≥ 3 × ULN and/or elevated total bilirubin ≥ 2 × ULN**: repeated liver chemistry tests (INR, fibrinogen, D-dimer [where available at institution], ALP, ALT, AST, GLDH, CPK, total bilirubin, direct bilirubin, indirect bilirubin) are required at 48 hours (-2/+12 hours) and 96 hours (-2/+12 hours) after the start of the infusion and every 48 hours (-2/+12 hours) thereafter until resolution of the event. If an event is not resolved within 96 hours the medical monitor shall be contacted. If GLDH cannot be performed locally, LDH will be analysed locally and a serum sample must be collected for central retrospective GLDH analysis. Refer to the Laboratory Manual for details.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets PHL criteria at any point during the study. The Investigator participates, together with the Sponsor, in review and assessment of these cases. Hy's Law (HL) criteria are met if there is no alternative explanation for the elevations in transaminases and total bilirubin levels.

If an unscheduled ECG is done at any time: troponin and an electrolyte panel* must be done to coincide with the ECG testing.

* can include: sodium, calcium, potassium, chloride, phosphate, magnesium.

If a participant is assessed as meeting PHL criteria, please refer to Appendix E.

CMV: All subjects will have CMV testing at Screening including serology testing for CMV immunoglobulin (Ig)G and CMV IgM and CMV DNA PCR testing. Subjects must have a negative result for CMV DNA PCR such that CMV DNA is not detected by PCR at Screening, to be eligible for the study. The Screening CMV serologies will be advisory only, to guide investigators in assessing the risk of new infection or reactivation of CMV while on study.

17.1.7 Other Safety Assessments

Monitoring for TLS per the SoA (Section 10.2) and prophylaxis for TLS are outlined in detail in Section 17.1.10.10.

Blood samples for CCI [redacted] will be collected per the SoA (Section 10.2) and as outlined in Section 17.9.6.

Additional safety assessment requirements include:

- **Echocardiograms (ECHOs):** In addition to Screening, an ECHO should be done within 14 days after an abnormal ECG finding (eg, T-wave inversion/flattening) or as soon as possible when clinically indicated. If an ECHO cannot be taken, a multigated acquisition (MUGA) scan to assess left ventricular ejection fraction (LVEF) will be done. In case of any T-wave abnormality, the ECHO (or MUGA) should be repeated at the 30-day SFU visit to address the question of recovery, during the off-treatment period.
- **CD4, CD8, CD19, CD16/NK** cell count and serum immunoglobulins (IgA, IgM, IgG)
  - Screening
  - Day 1 of Cycles 2, 4, 7, 9, 13, 16, 19
    - Predose
  - Every 6 months thereafter (predose)
  - 30-Day SFU

17.1.8 Electrocardiograms (ECGs)

Twelve-lead ECGs will be obtained after the participant has been resting semi-supine for at least 10 minutes before the times indicated. All ECGs should be recorded with the participant in the same physical position where possible.

If an abnormal ECG finding at Screening or baseline is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition. If a clinically significant abnormal ECG finding occurs on study, contact the Medical Monitor.

Single ECGs will be collected for local and central analysis at the following timepoints:

- Screening
- Cycle 1, Weeks 1 through 5 and Cycle 2, Day 1:
  - Predose (at the day of infusion prior to infusion)
  - End of infusion (within 30 minutes of end of infusion)
- Cycles 3+, Day 1 of each cycle:

  - Within 30 minutes after the end of infusion
- 30-Day SFU

Any abnormal finding in the ECG tracing will be evaluated by the Investigator and will be specifically documented and registered in the eCRF. Throughout the study, clinically relevant new findings or worsening of a pre-existing finding in the ECGs (parameters or abnormal findings in the tracing) must be considered an AE and must be recorded in the AE CRF form.

If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, potassium) and troponin I/troponin T must be done to coincide with the ECG testing. Note: either a troponin I or troponin T assay can be used per SoC at the respective hospital. If the hospital has both a SoC troponin I and troponin T assay available, the investigator shall use only one consistently for the duration of the study.

17.1.9 Follow-up

17.1.9.1 30-day SFU Visit

An SFU visit will be performed 30 (± 7) days from the time that both study drugs are permanently discontinued (see the SoA [Section 10.2]). Tumour assessments will be repeated at this visit if they have not been performed within 9 weeks if the participant discontinued before Week 53, or 12 weeks if the participant discontinued after Week 53.

17.1.9.2 Long-term Follow-up Visits

Participants who discontinue both study drugs before documented disease progression will be followed according to SoC until documented disease progression or the start of new anti-cancer therapy. Disease progression or start of new anti-cancer therapy will be captured in the eCRF. During this period, only information on any SAEs considered related to IP or study procedures will be collected. If a participant is unable to attend site for this visit, the long-term follow-up may be performed via phone call. Long-term follow-up visits will cease at disease progression or start of a new anti-cancer therapy, whichever comes first. The long-term follow-up will not apply to participants who withdraw consent or are lost to follow-up.

17.1.9.3 Survival Follow-up

All participants will be followed for survival until death, loss to follow-up, AstraZeneca closes the study, or withdrawal of consent, whichever occurs first. Participants will be followed for survival by telephone calls or clinic visits approximately every 3 months. Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants who received investigational product. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in

any attempts to collect vital status information. During this period, information will be collected in the eCRF on survival status and any new anti-cancer therapies, and on any SAEs considered related to study drug(s) or study procedures.

The follow-up calls/clinic visits for survival should occur every three months, starting 3 months after end of treatment/discontinuation (ie, 3/6/9/12 months after treatment). In case a shorter/longer interval between two follow-up calls occurs the frequency should return to the multiple of 3 months after treatment (eg, 3/6/9/12 months after treatment and so on).

In preparation for an analysis, survival calls will be made in the week following the data-cut-off for the analysis.

17.1.10 Prevention and Management of Safety Concerns for AZD4573 in Combination with Acalabrutinib

This section provides recommendations for treatment of potential toxicities associated with acalabrutinib, or the combination of AZD4573 with acalabrutinib, and guidance about modifying the doses of acalabrutinib and AZD4573 due to those toxicities. For complete safety information refer to CCI and Calquence United States Prescribing Information.

Generally, Grade 1 or 2 non-haematological and/or haematological toxicities do not require AZD4573 or acalabrutinib dose reductions and should be managed as medically indicated (with or without short dose interruptions) by the treating physician. Grade 3 and 4 toxicities require dose modifications, temporary treatment interruptions, or discontinuation of AZD4573 and acalabrutinib. These are described in Table 13 and Table 14.

17.1.10.1 Headache

Headache is an identified risk for acalabrutinib. Participants with headache should be managed per institutional guidelines with supportive care and diagnostic evaluations as clinically indicated.

Note: encouraging adequate hydration for participants experiencing headaches has anecdotally been helpful in some cases.

17.1.10.2 Diarrhoea

Diarrhoea is an identified risk for AZD4573 and acalabrutinib. Participants with diarrhoea during therapy should be managed per institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated. After excluding infectious aetiologies, symptomatic management should be considered. Participants experiencing prolonged or severe diarrhoea should be closely monitored and managed as appropriate if dehydration

and/or electrolyte abnormalities are observed. Participants should be made aware of the risk of possible overlapping toxicities of diarrhoea while receiving combination study treatments.

Prophylaxis for diarrhoea with atropine is strongly recommended for all participants enrolled into the study as an anti-cholinergic drug, administered at 0.5 mg subcutaneously 15 to 30 minutes prior to all scheduled AZD4573 infusions. In the event of multiple episodes of diarrhoea despite atropine prophylaxis, one additional atropine dose may be considered and administered as outlined above.

In addition, in the event of diarrhoea, participants should remain fully hydrated with additional IV fluids.

17.1.10.3 Nausea and Vomiting

Nausea and/or vomiting are identified risks for AZD4573 and acalabrutinib. Participants with nausea and/or vomiting during therapy should be managed per institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated. Participants experiencing prolonged or severe vomiting should be closely monitored and managed as appropriate if dehydration and/or electrolyte abnormalities are observed. Participants should be made aware of the risk of possible overlapping toxicities of nausea and vomiting while receiving combination study treatments.

Nausea and vomiting are considered important identified risks for AZD4573. Events of nausea and vomiting have been observed in approximately half of all participants dosed with AZD4573 and have occurred at all dose levels tested to date (except 3 mg). Prophylaxis with a 5-HT3 antagonist (eg, ondansetron ± dexamethasone) has been implemented in the Phase I study (D8230C00001) to help alleviate this toxicity.

Therefore, prophylaxis for nausea and vomiting is recommended as follows: administer dexamethasone 8 mg (IV administration preferable but orally also permitted) plus a 5-HT3 antagonist (e.g. ondansetron initially 8 mg to be taken before treatment, then 8 mg every 12 hours for up to 3 days) as anti-emetics for all participants, approximately 30 to 60 minutes prior to all scheduled AZD4573 infusions. Additional doses of dexamethasone 8 mg may be administered if deemed clinically warranted. In addition, in the event of vomiting, participants should remain fully hydrated with additional fluids. Participants experiencing prolonged or severe nausea and vomiting should be closely monitored and managed as appropriate if dehydration and/or electrolyte abnormalities are observed.

17.1.10.4 Hepatitis B Reactivation

Serious or life-threatening reactivation of viral hepatitis have been reported in participants treated with acalabrutinib. Therefore, participants who are anti-HBc positive, or have a known history of HBV infection, should be monitored every 3 months with a quantitative PCR test

for HBV DNA. Monitoring should continue until 12 months after last dose of acalabrutinib. Any participant with a rising viral load (above lower limit of detection) should discontinue acalabrutinib and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming acalabrutinib in participants who develop HBV reactivation.

17.1.10.5 Progressive Multifocal Leukoencephalopathy (PML)

Cases of PML have been reported in participants treated with acalabrutinib. Signs and symptoms of PML may include cognitive and behavioural changes, language disturbances, visual disturbances, sensory deficits, weakness, and coordination and gait difficulties.

If PML is suspected, hold further treatment with acalabrutinib until PML is excluded. A diagnostic evaluation may include (but is not limited to):

- Neurologic consultation
- Brain magnetic resonance imaging (MRI)
- PCR analysis for John Cunningham (JC) virus DNA in cerebrospinal fluid

If PML is confirmed, permanently discontinue acalabrutinib.

17.1.10.6 Haemorrhage

Bleeding events, some fatal, including CNS, respiratory, and gastrointestinal haemorrhage, have been reported in participants treated with acalabrutinib. Participants receiving antiplatelet or anticoagulant therapies may be at increased risk of haemorrhage and should be monitored for signs of bleeding. Should participants require either a vitamin K antagonist or combined administration of antiplatelet and therapeutic anticoagulation while on study, acalabrutinib treatment must be discontinued. As a precaution, it is suggested per protocol that acalabrutinib be withheld for at least 3 days pre- and post-surgery. Participants should be made aware of the risk of possible overlapping toxicities of haemorrhage while receiving both study treatments. Participants with haemorrhage should be managed per institutional guidelines or as clinically indicated. Coagulation should be monitored regularly as per the SoA. Avoidance of ibuprofen is advised.

17.1.10.7 Infections

Serious infections, including fatal events, have been reported in participants treated with acalabrutinib. Infection is an important potential risk for AZD4573 and an important identified risk for acalabrutinib. Participants should be made aware of the risk of possible serious infections while receiving combination study treatments. Investigators should be vigilant for signs of infection, especially opportunistic or fungal infections, and the possibility of hepatitis

B reactivation. Infections should be managed as per standard clinical practice. In case of Grade 3 infections, the guidelines provided in Table 13 should be followed.

17.1.10.8 Cytopenia

Haematological toxicities including neutropenia, anaemia, and thrombocytopenia have occurred in participants treated with acalabrutinib. Neutropenia is an important identified risk for participants treated with AZD4573 or acalabrutinib. Cytopenia should be considered an overlapping toxicity for AZD4573 and acalabrutinib. In the presence of CTCAE Grade 3/4 neutropenia/leucopoenia/thrombocytopenia/anaemia, participant's blood counts should be monitored, using local laboratories, at least every 48 hours until recovery.

In the clinical setting to date, Grade 3/Grade 4 neutropenia (~ 45% to 50%) has been observed in several participants with an onset around 24 hours after dosing AZD4573 monotherapy. Usually, neutrophils recovered spontaneously even without G-CSF.

Colony-stimulating factors including G-CSF, or pegylated G-CSF have been shown to work rapidly and may be used according to each Investigator site's institutional guidelines. Anti-infective prophylaxis including anti-fungal prophylaxis should be used according to institutional guidelines. Antiviral or cotrimoxazole prophylaxis may not be used unless CD4 helper cell counts are less than 100 to 200 per microlitre.

Primary prophylaxis with G-CSF is not generally recommended. Anti-infective prophylaxis (antibiotics and antifungals) should be given in accordance with local hospital and International National Comprehensive Cancer Network (NCCN)/European Society for Medical Oncology (ESMO)/American Society of Clinical Oncology (ASCO) guidelines.

Please refer to Table 13 for dose modifications due to haematological toxicities.

If the table indicates that the acalabrutinib dose should be reduced and the participant is already on 100 mg/day (see Table 12), acalabrutinib should be discontinued.

17.1.10.9 Liver Chemistry Test Abnormalities and the Risk of Liver Injury

Transaminase elevations are an important potential risk for patients treated with acalabrutinib, and an important identified risk for participants treated with AZD4573. Reactivation of hepatitis B infection has been observed in patients treated with acalabrutinib. Participants should be made aware of the risk of possible overlapping toxicities of transaminase elevations while receiving both drugs. Evidence of abnormal liver chemistry should be monitored as per the protocol guidelines. Increased levels of AST, ALT, or serum bilirubin should trigger an investigation of the cause, which may include viral infection or disease progression with liver infiltration. The Investigator should consider whether the abnormal liver chemistry meets the criteria for expedited reporting.

Bilirubin increase with transaminase increase is included as an important identified risk for AZD4573. Biochemical changes of increased transaminases with concomitant increase in bilirubin fulfilling criteria for Hy's law have been observed in participants treated with AZD4573. These events resolve rapidly and have to date not been associated with any adverse clinical sequelae or lasting liver damage. Upon rechallenge with AZD4573, there is no consistent pattern of recurrence, nor is there any consistent increase in severity of the events. As such, while the events follow the biochemical definition of Hy's law, the clinical pattern is rapidly self-limiting and does not seem to predict any lasting liver damage.

Participants who experience elevated ALT/AST ≥ 3 × ULN and/or elevated total bilirubin ≥ 2 × ULN after AZD4573 dosing must be closely monitored with repeated liver chemistry tests (INR, fibrinogen, D-dimer [where available at institution], ALP, ALT, AST, GLDH (if a GLDH test cannot be performed at the site or locally, LDH will be sufficient), CPK, total bilirubin, direct bilirubin, indirect bilirubin) are required at least every 48 hours (-2/+12 hours) after the start of the infusion and until resolution of the event. CCI [redacted] will also be collected (see Section 17.9.6).

If bilirubin fails to resolve within 96 hours (-2/+12 hours) or transaminases fail to resolve within 7 days, or if the event is associated with significant clotting abnormality or clinical symptoms of liver disease, study treatment must be permanently discontinued (the participant remains on study for the 30-day SFU and long-term follow-up [LTFU] visits), and the event must be immediately communicated to AstraZeneca.

For guidance on treating liver toxicity, please refer to Table 14 of this protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets PHL criteria at any point during the study.

Please refer to Appendix E for the process to be followed to identify and appropriately report cases of PHL. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

The Investigator will participate, together with the Medical Monitor, in review and assessment of PHL events to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

Regarding the hepatic toxicity events encountered to date with AZD4573, it has been observed that while the biochemical changes of increased transaminase with concomitant elevation in bilirubin seen in some participants could be classified as HL by its strict definition, they do not follow a pattern that is consistent with true HL predictive of hepatic injury, and are therefore 'PHL' cases. The events are rapidly resolved and to date have not led to any clinical sequelae or lasting hepatic injury. Repeated dosing with AZD4573 following these events has demonstrated that there is no consistent pattern of recurrence and no consistent increase in severity of the events if they do recur.

Available transcriptomic and clinical pathology data from the Phase I, FTIH study of AZD4573 monotherapy (D8230C00001) suggest the presence of an acute phase response in participants showing signs of liver injury. Thus, anti-inflammatory prophylaxis with steroids (eg, dexamethasone) could be expected to have a beneficial effect on incidence and severity of adverse effects on the liver related to AZD4573.

While, in the absence of a suitably-sized control group without prophylactic steroid administration, there is no confirmatory evidence for a positive effect of dexamethasone on liver safety profiles from available Phase I clinical data as yet, assessment of ALT changes from baseline versus cumulative dexamethasone dose suggests a possible trend towards a negative correlation, ie, higher dexamethasone doses being associated with smaller increases in ALT post-baseline.

17.1.10.10 Tumour Lysis Syndrome (TLS)

Tumour lysis syndrome is an important identified risk for AZD4573 and an identified risk for acalabrutinib. **TLS prophylaxis is mandatory for <u>all</u> participants** starting 3 days before the first dose of AZD4573, which should be followed in addition to institutional guidelines.

Tumour lysis syndrome is characterised by the rapid and/or massive release of intracellular constituents (potassium, phosphorus and nucleic acids that can be metabolised to uric acid) following tumour cell lysis, resulting in life-threatening complications including acute kidney injury, arrhythmias, and neurological complications. While TLS can be seen in solid tumours, it is most prevalent in haematological malignancies, particularly bulky, chemosensitive diseases such as AML. Prevention and management of TLS is dependent on risk stratification, and risk-based prophylaxis and management (Howard et al 2011). Participants identified with TLS potential per published risk guidelines (Coiffier et al 2008; Table 16) should be provided with adequate hydration, pharmacological pre-treatment with allopurinol or rasburicase, and be carefully monitored for development of TLS.

Instructions for TLS prophylaxis are presented in Section 17.1.10.10.1, instructions for management of hydration are presented in Section 17.1.10.10.2, and instructions for

monitoring and maintenance of TLS are presented in Section 17.1.10.10.3. The Howard modification of Cairo-Bishop criteria for clinical and laboratory TLS are included in Appendix F.

Laboratory or clinical TLS (please refer to Appendix F for definitions) may trigger dose modification in accordance with guidelines provided in Table 13.

17.1.10.10.1 TLS Prophylaxis

Tumour lysis syndrome prophylaxis is mandatory for **all** patients starting 3 days before the first dose of AZD4573. TLS prophylaxis is mandatory for all infusions as outlined below in Table 16, which provides TLS prophylaxis guidance that should be followed in addition to institutional guidelines. In the event of a discrepancy between the protocol guidelines for the management of TLS and the institutional guidelines of a given Investigator/centre, the Investigator should discuss with the Medical Monitor.

In addition to the criteria outlined in Table 16 below, any patient with creatinine clearance (CrCL) < 80 mL/min must be considered at higher risk of developing TLS and managed appropriately.

TLS prophylaxis/management with rasburicase/allopurinol and IV fluid is permitted at any time during screening and treatment, however rasburicase and allopurinol must not be co-administered (Howard et al 2011; Howard et al 2016; Jones et al 2015).

Table 16 Mandatory TLS Prophylaxis Guidance (in Addition to Institutional Guidance)

Type of Cancer	Intermediate/High Risk
NHL	DLBCL OR Any LN ≥ 5 cm
	Prophylaxis
Hydration[a]	Oral (1.5-2.0 L/day) plus additional IV fluid: Normal saline 500 mL over 2-4 h prior to AZD4573, then 100-175 mL/h as tolerated to maintain urine output
Antihyperuricemics	Allopurinol 300 mg orally QD beginning 3 days prior to AZD4573 and continuing at least through the end of Week 1[b]. Consider prophylactic rasburicase[c] if baseline uric acid is elevated above ULN[d], LDH > 2 × ULN, or high tumour burden/leukemic cells

[a] Administer more aggressive IV fluid hydration for any patient who cannot tolerate or maintain oral hydration.

[b] Administration of allopurinol should not be stopped at the end of Week 1, however the dose or frequency of administration may be reduced after discussion with the Medical Monitor.

[c] The recommended dose for rasburicase is 0.20 mg/kg IV over 30 minutes. Rasburicase is contraindicated in patients with G6PD deficiency, so patients at higher risk for G6PD deficiency (eg, African or Mediterranean ancestry) should be screened for this condition prior to starting rasburicase. Rasburicase and allopurinol must not be co-administered.

[d] Uric acid levels should be < ULN before each dosing of AZD4573.

Notes: Adequate supportive therapy as per institutional guidelines should be given for all toxicities.
TLS prophylaxis/management with rasburicase/allopurinol and IV fluid is permitted at any time during screening and treatment. Rasburicase and allopurinol must not be co-administered.
Abbreviations: DLBCL = diffuse large B-cell lymphoma; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenous; LDH = serum lactate dehydrogenase; LN = lymph node; NHL = non-Hodgkin lymphoma; QD - once daily; TLS = tumour lysis syndrome; ULN = upper limit of normal.
Modified from Coiffier et al 2008.

17.1.10.10.2 Management of Hydration

Adequate fluid intake for all patients enrolled into the study is mandatory, in particular, around the times of AZD4573 dosing.

All patients are **mandated** to receive IV fluid hydration with normal saline (NaCl 0.9%). For patients at intermediate or high risk for TLS, normal saline 500 mL should be administered over 2 to 4 hours prior to AZD4573 and then continued at a rate of 100 to 175 mL/h as tolerated to maintain urine output.

In case of diarrhoea/nausea/vomiting, more aggressive IV fluid hydration may be needed as clinically indicated. Patients are also encouraged to drink enough fluid before and after each dosing. Please use diuretics carefully, do not use them prophylactically, only if patients have signs of hyper-hydration.

17.1.10.10.3 TLS Prophylaxis, Monitoring, and Management

Please refer to Appendix F for definitions of the Howard modification of Cairo-Bishop criteria for clinical and laboratory TLS.

All patients will receive TLS prophylaxis during the intra-patient ramp up and be monitored for TLS during the first 24 hours post start of dose. Monitoring for TLS includes checking potassium, calcium, phosphate, uric acid, and creatinine. Fluid balance must be monitored according to institutional standards.

Patients 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). If a patient has no signs of laboratory TLS at the 6-hour TLS monitoring assessment, the patient may leave the clinic after the collection of other laboratory samples, as per the SoA, at 7 hours after the start of the infusion and managed as an outpatient, at the discretion of the Investigator. These patients must return to the clinic the next morning to complete the 24 hour TLS monitoring period as per the SoA (Cycle 1 Weeks 1-3). Patients with TLS at the 6-hour TLS monitoring assessment must be admitted for in-patient TLS monitoring for a minimum of 24 hours after the start of the infusion and monitored every 4 to 6 hours during this time (or more frequently if clinically indicated).

Sites retain the option to hospitalise patients based on clinical judgement, despite normal TLS laboratory results 6 hours after the start of the infusion. Admitting the patient for subsequent dose administrations will be done at Investigator discretion.

Any hospitalisation due to occurrence of an AE must be reported as an SAE, per definition. However, if hospitalisation is purely for the purposes of extended observation then this does not qualify as an SAE and does not need to be reported.

For all patients, results of safety laboratory testing (haematology and clinical chemistry at a minimum) must be available within 72 hours prior to dosing and must be reviewed by the Investigator prior to each administration of AZD4573.

In particular, the uric acid level must be < ULN prior to the start of each AZD4573 infusion.

It is strongly recommended that for all patients with elevated uric acid (hyperuricaemia) and intermediate/high risk of TLS, rasburicase (0.20 mg/kg/d IV over 30 minutes) should be administered as prophylaxis prior to AZD4573 and repeated as clinically indicated thereafter as per local standard.

NOTE: If hyperuricaemia is present at Screening and/or during intra-patient ramp up, SoC therapy for hyperuricaemia should be administered (including IV fluid and

rasburicase or allopurinol) to reduce the uric acid levels to < ULN before each administration of AZD4573. Rasburicase and allopurinol must not be co-administered.

Any patient developing laboratory TLS must be treated promptly for electrolyte abnormalities (such as hyperkalaemia) to prevent arrhythmias/seizures and for elevated uric acid (hyperuricaemia) with rasburicase (0.20 mg/kg/d IV over 30 minutes for up to 5 days) to prevent acute renal failure and monitored closely for signs of progression to clinical TLS.

If these measures are inadequate, then haemodialysis represents definitive therapy and should be initiated promptly.

Any patient with hyperkalaemia should receive cardiac monitoring with continuous telemetry for ECG changes associated with potentially life-threatening arrhythmias.

Patients with TLS or suspicion of TLS will remain in hospital to undergo additional investigations until the TLS has resolved.

In patients at high risk of TLS based on high tumour burden/bulky disease (> 10 cm), high proliferation rate (LDH > 2 x ULN), and/or impaired renal function (Coiffier et al 2008), 24-hour hospitalisation for TLS monitoring is recommended during the intra-patient ramp up.

17.1.10.11 Second Primary Malignancies

Second primary malignancies, including non-skin cancers, have been reported in patients treated with acalabrutinib. The most frequent second primary malignancy was skin cancer (squamous cell carcinoma of the skin). Monitor patients for the appearance of skin cancers. If a patient develops a second primary malignancy (other than non-melanoma skin cancer), discontinue acalabrutinib. Patients with a second primary malignancy should be managed according to institutional guidelines with diagnostic evaluations as clinically indicated.

17.1.10.12 Atrial Fibrillation/Flutter and Sinus Tachycardia

Atrial fibrillation/flutter have been reported in patients treated with acalabrutinib. Atrial fibrillation has also been observed in patients treated with AZD4573, although positive causality has not been established.

CCI [redacted]

17.1.10.13 Infection/Bone Marrow Toxicity with Peripheral Effect / Lymphoid Tissue Hypocellularity

Infection/bone marrow toxicity with peripheral effect/lymphoid tissue hypocellularity is an important potential risk for AZD4573, based on findings in preclinical studies. Severe infection is considered as an important risk with the combination therapy (Section 17.1.10.7).

As observed in preclinical studies, this important potential risk refers to haematological changes (decreased platelets, red blood cell count/haematocrit, reticulocytes, neutrophils, lymphocytes) that may be/may not be accompanied by secondary infections.

AEs of thrombocytopenia should be managed as deemed appropriate by the Investigator as per standard institutional guidelines and in some cases, management of thrombocytopenia may require platelet transfusions, again these should be done according to local hospital guidelines. If indicated, transfusions or growth factors can be administered during the screening period, but such cases of deterioration of haematological function must be discussed with the Medical Monitor, to confirm start of study treatment.

Common treatable causes of anaemia (eg, iron, vitamin B12, or folate deficiencies and hypothyroidism) should be excluded. In some cases, management of anaemia may require blood transfusions which should be given as per local institutional guidelines.

17.1.10.14 Pancreatic and Cortical Adrenal Injury (as well as Surveillance for Renal, Thymus, and Spleen Toxicity)

Pancreatic injury and cortical adrenal injury are potential risks for AZD4573 based on preclinical observations, however, to date, there are no clinical data suggestive of these risks, but safety surveillance will continue.

Regular complete blood counts, clinical chemistry and coagulation tests will be performed throughout the conduct of the study to monitor for any abnormal laboratory parameters, for example; monitoring of lipase and amylase levels for potential pancreas toxicity, creatinine values and regular urinalysis testing for kidney function, potassium, sodium, cortisol levels along with adrenocorticotropic hormone levels for adrenal glands and thyroid-stimulating hormone (TSH) for any thyroid toxicity.

17.1.10.15 Drug-Drug interactions

Specific drug-drug interaction studies have not yet been performed for AZD4573. For guidance please refer to Section 15.11.

Acalabrutinib may be affected by agents that reduce gastric acidity (antacids or proton-pump inhibitor). Acalabrutinib is not a strong direct inhibitor or inducer of CYP isoforms and is therefore unlikely to perpetrate drug-drug interactions through affecting CYP isoforms (see Section 15.11).

17.1.10.16 Myocardial Ischaemia and Heart Rate Increased

Myocardial ischaemia and heart rate increased are considered potential risks for AZD4573. There has been an isolated case report of possible myocardial infarction in association with AZD4573, but positive causality could not be established. The same patient experienced heart

rate increase during the event of ST-segment elevation myocardial infarction. A thorough evaluation of all participants dosed to date has not revealed any further cases suggestive of myocardial ischaemia or other cardiovascular toxicity causally related to AZD4573 administration.

Safety surveillance related to this potential toxicity will include ECG and troponin I/troponin T measurements for all patients as described in the SoA (Section 10.2). ECG and troponin I/troponin T measurements must be performed for all patients who develop symptoms suggestive of myocardial ischaemia. Note: either a troponin I or troponin T assay can be used per SoC at the respective hospital. If the hospital has both a SoC troponin I and troponin T assay available, the investigator shall use only one consistently for the duration of the study.

17.1.10.17 Management of Other Events: Infusion Site Reactions

As with other drugs administered intravenously, local infusion site reactions (eg, infusion pain, infusion site reaction, skin or vein irritation) may occur and these can be managed according to local institutional guidelines. Implantable port insertions (eg, Portacath) may be considered.

17.2 Adverse Events and Serious Adverse Events

A formal assessment of AEs will occur at the visits marked in the SoA (Section 10.2), but AEs reported at any time during the study must also be recorded in the eCRF.

Please refer to Section 8.2.

17.2.1 Adverse Events of Special Interest for Acalabrutinib

The following events are Adverse Events of Special Interest (AESIs) for acalabrutinib and must be reported to the Sponsor expeditiously, irrespective of regulatory seriousness criteria or causality:

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

Adverse events of special interest for AZD4573 are described in Section 8.2.11.

17.3 Overdose

Please refer to Section 8.3 for general information and information related to AZD4573.

An acalabrutinib overdose is defined as any dose that is higher than the investigated dose. For any patient experiencing an acalabrutinib overdose, observation for any symptomatic side

effects should be instituted, and vital signs, biochemical and haematological parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion of acalabrutinib is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

17.4 Efficacy Assessments

All assessments of anti-tumour activity will be done by the investigators using standard response criteria as specified below (Table 18).

17.4.1 Disease Assessment Criteria

Disease staging at baseline for DLBCL and MZL will be done by a modified Ann Arbor classification system (Table 17; Cheson et al 2014). Response assessments will be done by the investigator using standard Lugano 2014 response criteria as specified in Table 18.

Table 17 Lugano Modification of Ann Arbor Staging System (for Primary Nodal Lymphomas)

Stage		Involvement	Extranodal (E) Status
Limited	I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
	II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II Bulky Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors		II as above with “bulky” disease	Not applicable
Advanced	III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
	IV	Additional noncontiguous extralymphatic involvement	Not applicable

Note: Extent of disease is determined by PET-CT for avid lymphomas and CT for nonavid histologies.
Tonsils, Waldeyer’s ring, and spleen are considered nodal tissue.
Abbreviations: CT = computed tomography; PET = positron emission tomography.
Reproduced from Table 2.

Table 18 The Lugano Response Criteria for Non-Hodgkin's Lymphoma

Response and Site	PET-CT-Based Response	CT-Based Response
Complete:	**Complete metabolic response:**	**Complete radiologic response (all of the following):**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[b,c] It is recognised that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial:	**Partial metabolic response:**	**Partial remission (all of the following):**
Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default valve
	At end of treatment, these findings indicate residual disease	When no longer visible 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None

Response and Site	PET-CT-Based Response	CT-Based Response
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease:	**No metabolic response:**	**Stable disease:**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease:	**Progressive metabolic disease:**	**Progressive disease requires at least 1 of the following PPD progression:**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm

Response and Site	PET-CT-Based Response	CT-Based Response
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of pre-existing nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another aetiology (eg, infection, inflammation). If uncertain regarding aetiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

[a] The Lugano 2014 criteria are used in this study for disease assessment. In line with these criteria, it should be clarified that the study definition of CMR is a Deauville score 1-3.

[b] A score of 3 in many participants indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy of myeloid growth factors).

[c] PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Abbreviations: 5PS = 5-point scale; CT = computed tomography; CMR = complete metabolic response; FDG = fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LDi = longest transverse diameter; MRI = magnetic resonance imaging; PET = positron-emission tomography; PPD = product of the perpendicular diameters; SDi = shortest axis perpendicular to LDi; SPD = sum of the product of the diameters. Cheson et al 2014

17.4.2 Disease Assessment Schedule

Baseline tumour assessments will be performed using radiologic imaging by computed tomography (CT) with contrast and positron- emission tomograph (PET)-CT during the screening period. CT scans with contrast will cover neck, chest, abdomen, pelvis and any other disease sites; PET scans will cover the whole body from base of skull to mid-thigh.

Radiologic scans (ie, contrast CT) and PET scans will be performed as specified in Table 19, to confirm CR or as clinically indicated. Unscheduled radiologic scans may be performed at Investigator discretion if deemed clinically indicated.

Table 19 Radiologic Scans and PET Scans for Tumour Assessments

Timepoints		Required Radiologic Scans[a]	
Screening		Contrast CT	PET
During study[b]	After 8 weeks (~2 cycles)	Contrast CT	PET
	After 17 weeks (~5 cycles)	Contrast CT	
	After 26 weeks (~8 cycles)	Contrast CT	PET
	After 38 weeks (~12 cycles)	Contrast CT	
	After 50 weeks (~16 cycles)	Contrast CT	PET
	After 62 weeks (~20 cycles)	Contrast CT	
	After 74 weeks (~24 cycles)	Contrast CT	PET
	After 86 weeks (~28 cycles)	Contrast CT	
	After 98 weeks (~32 cycles)	Contrast CT	PET
	Every 12 weeks (~4 cycles) thereafter until the end of the study	Contrast CT	
	Every 24 weeks (~8 cycles) thereafter until the end of the study	Contrast CT	PET
30-day Follow-up visit[c]		Contrast CT	PET

[a] Following complete metabolic response, subsequent scheduled PET assessments are no longer mandatory.
[b] Window of ± 1 week for all timepoints.
[c] Tumour assessments will be repeated at this visit for discontinued participants if not previously performed within the required timeframe ie, 9 weeks for participants that discontinued before or during Week 26, and 12 weeks for those that discontinued after Week 26.

If a PET-CT is not available, an independent PET and a diagnostic quality CT scan (with contrast) can be used. If PET and CT scans are done on the same day, the PET must be performed prior to the contrast-enhanced CT not to compromise the PET read-out.

Post-screening, the CT portion of a PET-CT (without contrast) may replace a contrast CT per local institutional practice; however, certain radiographic requirements are needed for acceptance, as described in the Site Radiology Manual, provided separately from this protocol.

Where contrast CT is contraindicated or unobtainable, MRI or CT (without contrast) with diagnostic quality (sufficient resolution to allow bi-dimensional measurements) may be used instead. In cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations.

Following complete metabolic response, subsequent scheduled PET assessments are no longer mandatory. For participants with baseline hepatosplenomegaly, the cranial-caudal measurement of the spleen and longest diameter of the liver will be assessed at Screening and all subsequent response evaluations.

All response assessments will be made by the Investigator. All images for the assessment of response will be collected and stored for central review.

Participants should have radiographic tumour measurements done at the participating study centre or an acceptable alternate imaging facility using an identical imaging protocol and similar equipment. The same imaging equipment should be used for all scans whenever possible. The same radiologist should be assigned to read all the scans for a given participant throughout the study.

Participants who discontinue study intervention for reasons other than PD will continue to be scanned for disease response following the same schedule until documented PD, regardless of the start of new anti-lymphoma treatment.

17.4.3 Bone Marrow Assessments

For all patients, bone marrow biopsy and aspirate samples are required for local standard disease profiling (eg, immunohistochemistry, flow cytometry, cytogenetics, fluorescence in situ hybridisation [FISH]). Bone marrow biopsies/aspirates will be collected:

- at Screening (before first dose of AZD4573)
- during the study as part of disease assessment (Cheson et al 2014), when indicated
- as clinically indicated (per SoC)

If bone marrow/aspirate samples are collected on a AZD4573 dosing day, collection should preferably take place pre-infusion. If this is not possible, the collection should take place between 2 hours and 4 hours after the start of the infusion.

If a bone marrow biopsy/aspirate cannot be performed, the Investigator must document in the patient's medical notes the reason why the procedure cannot be performed. Archival bone marrow biopsy/aspirate can replace the assessment performed at Screening if necessary, after discussion with the Sponsor's Medical Monitor.

Bone marrow biopsies/aspirates will be read at each site's local laboratory. The results will be entered into the eCRF.

CCI [redacted]

17.4.4 Tumour Assessment

Initial disease assessments for DLBCL include:

- Staging by Ann Arbor classification (Cheson et al 2014: see Table 17).
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen.
- Complete blood count, platelets, differential, chemistry profile, lactate dehydrogenase
- Whole-body fluorodeoxyglucose (FDG)-PET/CT scan.
- Brain imaging (MRI with contrast preferred). MRI of the brain will be performed at Screening only if there is a prior history of CNS involvement or if there are neurologic signs or symptoms present.
- Bone marrow biopsy and aspirate (Section 17.4.1).

DLBCL response criteria: Lugano Response Criteria for Non-Hodgkin's Lymphoma (Cheson et al 2014, see Table 18).

Baseline tumour assessments will be performed using radiologic imaging by CT with contrast and PET-CT covering neck, chest, abdomen, and pelvis within 30 days before the first dose of AZD4573 (Table 19). For participants with baseline hepatosplenomegaly, the cranial-caudal measurement of the spleen and longest diameter of the liver will be assessed at screening and all subsequent response evaluations. Unscheduled radiologic scans may be performed at investigator discretion if deemed clinically indicated. Magnetic resonance imaging may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable. In cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response

evaluations.

For MZL patients with FDG-avid disease at baseline, disease response to study treatment will be based on both PET and CT-based criteria. For MZL patients with no FDG-avid disease at baseline, disease response to study treatment will be based CT-based criteria only. After the first year of treatment in MZL patients, Lugano tumour assessment with CT with contrast every 24 weeks is sufficient, and additional CT and PET assessments can be performed as clinically indicated.

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 (Cheson et al 2014). See Table 19.

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

CT scans

Bi-dimensional measurements will be recorded for lymph nodes ≥ 1.5 cm in longest diameter in the eCRF. Up to a maximum of 6 dominant, measurable lymph nodal lesions should be assessed as target lesions. These nodes or masses should be selected according to all of the following:

- They should be clearly measurable in at least two perpendicular dimensions.
- If possible, they should be from disparate regions of the body.
- They should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

The perpendicular long and short axis diameters will be measured and recorded in the transverse plane at baseline and follow-up. When appropriate, measurable extranodal disease, defined as extranodal lesions (eg, hepatic nodules) with the longest diameter ≥ 1.0 cm, may be included in the 6 representative, measured lesions.

For the selected target lymph nodal lesions, the sum of the product of the perpendicular diameters will be calculated with the percentage change from baseline for assessment of response and nadir for assessment of progression.

All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, gastrointestinal, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites) and should be factored into overall response assessment.

Visual interpretation of PET-CT scans

The International Working Group criteria for reviewing PET scans were based on visual interpretation, using mediastinal blood pool as the comparator. The current recommendation is to use the 5-point scale (Cheson et al 2014).

Assessment of non-measurable lesions

An overall assessment for all other non-target lesions of present, absent, or present with progression will be recorded and factored into response assessment.

Assessment of new lesions

Appearance of any new lesions more than 1.5 cm in any axis during or at the end of therapy, even if all other lesions are decreasing should be considered progression.

Increased FDG uptake in a previously unaffected site should only be considered progression after confirmation with other modalities (eg, CT, MRI, or X-ray).

In patients with no history of pulmonary lymphoma, new nodules identified by CT are benign and should be considered negative for lymphoma. These lesions typically represent infectious or inflammatory lesions; therefore, if FDG positive, should not be considered positive for lymphoma in the absence of confirmatory tests, (eg, histology).

The presence or absence of new lesions will be recorded in the eCRF.

17.5 Human Biological Samples

Please refer to Section 8.5 for general information on collection and handling of biological samples.

17.6 Pharmacokinetics

Venous blood samples for determination of concentrations of AZD4573 and acalabrutinib and its metabolite ACP-5862 will be taken as the times presented below (see Section 10.2).

Samples for PK should be collected from the arm that is not used for the infusion where possible. If this is not possible, then separate lines should be used for drug infusion and sampling. If there is no other option than to use a central line (PICC-line) for drug administration/sample collection, it is mandatory this is a multi-lumen line. This information should be recorded where possible. AZD4573 should be administered using a different lumen

from the one which is used for sample collection. The sample collection lumen needs to be flushed twice prior to collecting the sample. AZD4573 administration needs to be paused during the time the samples are collected to prevent sample contamination.

Sample collection date, time, and exact dosing will be recorded for both AZD4573 and acalabrutinib. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

On the day of PK collection, acalabrutinib capsules should be brought to site by the patient and taken within 5 minutes before initiation of AZD4573. The actual date and time of AZD4573 and acalabrutinib dosing will be recorded.

If the patient, in error, takes acalabrutinib at home before coming to the site on the day of PK collection, PK sampling should be conducted at the timepoints listed according to AZD4573 dose provided that the exact time of acalabrutinib dosing was recorded. If there is no record for acalabrutinib dosing, PK should not be collected.

Part A

Plasma samples for PK analysis will be taken at the following time points:

- Cycle 1 of Weeks 1 to 3 and Cycle 2, Day 1
  - Predose (within 2 hours prior to AZD4573 and acalabrutinib administration)
  - 1 hour (± 15 minutes) after the start of the infusion
  - 2 hours (± 15 minutes) after the start of the infusion
  - 4 hours (± 30 minutes) after the start of the infusion
  - 7 hours (± 1 hour), after the start of the infusion
  - 24 hours (± 1 hour) after the start of the infusion (and prior to acalabrutinib dosing)

The timing and frequency of the PK samples may be adjusted during the study, dependent on emerging data, to ensure appropriate characterisation of the plasma concentration-time profiles.

Part B

Plasma samples for PK analysis will be taken at the following time points:

- Cycle 1 of Weeks 1 to 3 and Cycle 2, Day 1
  - Predose (within 2 hours before AZD4573 and acalabrutinib administration)
  - 2 hours (± 15 minutes) after the start of the infusion

- 4 hours (± 30 minutes) after the start of the infusion

The timing of these samples may be adjusted dependent upon ongoing PK analysis and interpretation.

17.6.1 Determination of Drug Concentration

Samples for determination of AZD4573, acalabrutinib, and its metabolite ACP-5862 concentrations in plasma will be analysed by Covance Laboratories on behalf of AstraZeneca, using appropriate validated bioanalytical methods. Full details of the analytical methods used will be described in a separate bioanalytical report.

All samples still within the known stability of the analytes of interest (ie, AZD4573) at the time of receipt by the bioanalytical laboratory will be analysed. Incurred sample reproducibility analysis or additional assay development work, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate bioanalytical report.

17.7 Pharmacodynamics

17.7.1 Collection of Samples (Part A and Part B)

Whole blood samples will be collected and immediately processed within 30 minutes on site for CCI [redacted]

In addition, whole blood will be collected at limited timepoints to analyse pharmacodynamic readouts for acalabrutinib.

Pharmacodynamic (whole blood) samples will be collected at the following timepoints (see Section 10.2):

Pharmacodynamic Samples for AZD4573 CCI [redacted]

Part A

- Cycle 1, Week 1 and Week 2:
  - Predose (within 2 hours prior to dosing)
  - 2 hours (± 15 minutes) after the start of the infusion

  - 4 hours (± 30 minutes) after the start of the infusion
  - 24 hours (± 2 hours) after the start of the infusion (and prior to acalabrutinib dosing)
- Cycle 1, Week 3:
  - Predose (within 2 hours prior to dosing)
  - 2 hours (± 15 minutes) after the start of the infusion
  - 4 hours (± 30 minutes) after the start of the infusion
  - 7 hours (± 1 hour) after the start of the infusion
  - 24 hours (± 2 hours) after the start of the infusion (and prior to acalabrutinib dosing)

Part B

- Cycle 1, Weeks 1 to 3:
  - Predose (within 2 hours prior to dosing)
  - 2 hours (± 15 minutes) after the start of the infusion
  - 4 hours (± 30 minutes) after the start of the infusion
  - 7 hours (± 1 hour) after the start of the infusion
  - 24 hours (± 2 hours) after the start of the infusion (and prior to acalabrutinib dosing)

Pharmacodynamic Samples for Acalabrutinib (whole blood) (Part A and B)

- Cycle 1, Week 1
  - Predose (within 2 hours prior to dose and prior to acalabrutinib dosing)
- Cycle 1, Week 4
  - Predose (within 2 hours prior to dose and prior to acalabrutinib dosing)

CCI must be collected at each sample at each pharmacodynamics timepoint once patients have reached the target dose. Refer to instructions in the Laboratory Manual.

Note: The timing of these samples may be adjusted dependent upon ongoing PK and pharmacodynamic analysis and interpretation.

For storage, re-use and destruction of pharmacodynamic samples, please refer to Appendix C.

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

17.8 Exploratory CCI [redacted] Samples (Part A and Part B)

CCI [redacted] samples will be collected from all patients to assess exploratory CCI [redacted] These samples will be collected as per the timepoints in Section 10.2.

Table 20 CCI [redacted] Sampling Schedule (All Patients)

Day	Timing for CCI [redacted]	Window
Screening	At any screening visit	Not applicable
Cycle 1, Weeks 1-3	Predose	Within 2 hours before the start of the infusion
	4 hours after the start of the infusion	± 30 minutes
	7 hours after the start of the infusion	± 1 hour
	24 hours after the start of the infusion	± 1 hour
CCI [redacted]	48 hours after the start of the infusion	-2/+12 hours
	96 hours after the start of the infusion	-2/+12 hours
	Predose the following infusion	Within 4 hours before the start of the infusion
	Each timepoint where chemistry panel testing is performed	N/A
Any visit from Cycle 1, Week 4 onwards CCI [redacted]	Same schedule as Cycle 1, Weeks 1-3	N/A

For all patients, CCI [redacted] samples will be collected during Cycle 1, Weeks 1 to 3. In addition, if a patient has CCI [redacted] samples should also be taken at 48 hours and 96 hours after the start of the infusion (-2/+12 hours), predose the following infusion (within 4 hours), and whenever chemistry panel testing is being performed, until resolution of the event.

CCI [redacted] sampling should be performed using the timepoints at least at 48 hours and 96 hours after the start of the infusion (-2/+12 hours) as outlined in Table 20 (excluding Screening sample).

17.9 Exploratory Whole Blood Analyses Samples

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

Samples for CCI [redacted] are required and will be collected from all patients.

Mandatory whole blood samples will be collected from all patients as per the schedule in Table 21 and the sections below.

Table 21 Exploratory Whole Blood Analyses Samples (All Patients) - MODULE 1

Samples	Timepoints[a]																		
	Screening	C1 Week 1			C1 Week 2			C1 Week 3			C1 W5	C2 D1	C2 D15	C3 D1	C5 D1	C6 D1	C7 D1	Tumour Assessment Scans[b]	EOT[c]
		Pre	Post (2h)	24h	Pre	Post (2h)	24h	Pre	Post (2h)	24h	Pre	Pre	Pre	Pre	Pre	Pre	Pre		
CCI	X	X						X			X	X	X	X	X	X	X	X	X
CCI	X	X						X			X	X	X	X	X	X	X	X	X
CCI	X	X						X		X[B]		X	X	X	X		X	X	X
CCI	X	X						X				X	X					X	X
CCI	X[B]	X[B]										X[B]		X[B]	X[B]		X[B]	X[B]	X[B]
CCI	X	X	X	X	X	X	X	X	X	X		X		X	X		X	X	X

[a] Timepoints include the following windows: pre-dose = within 2 h prior to dosing; post-dose = 2 h (± 15 min) after start of infusion, and 24h = 24 h(± 2 h) after start of infusion.

[b] Every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion)

[c] Disease progression/End of Treatment; if not collected at End of Treatment, the sample should be collected at the 30d Safety Follow-Up visit

[d] CCI

[e] CCI

[f] CCI

[g] CCI

[h] CCI

Note: For all analytes, if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

Abbreviations: [B] = Part B only; C1W5 = Cycle 1 Week 5; C2D1 = Cycle 2, Day 1; EOT= end of treatment; CCI CCI post = post-dose; pre = pre-dose; 24h = 24 h after infusion; SFU = safety follow-up.

17.9.1 Whole Blood for Exploratory [redacted] (Part A and B)

Mandatory whole blood samples to enable exploratory [redacted] analysis will be collected as specified below. Note: Collection time begins with the start of the infusion.

- Screening
- Cycle 1, Weeks 1, 3, and 5:
  - Predose (within 2 hours prior to dosing)
- Cycle 2, Days 1 and 15:
  - Predose (within 2 hours prior to dosing)
- Day 1 of Cycles 3, 5, 6, and 7:
  - Predose (within 2 hours prior to dosing)
- Every scheduled or unscheduled tumour assessment scan (if on day of infusion, collect pre-infusion)
- Disease progression/End of treatment - if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

17.9.2 Whole Blood for [redacted] Analysis (Part A and B)

Mandatory whole blood samples [redacted] Note: Collection time begins with the start of the infusion.

- Screening
- Cycle 1, Weeks 1, 3, and 5:
  - Predose (within 2 hours prior to dosing)
- Cycle 2, Days 1 and 15:
  - Predose (within 2 hours prior to dosing)
- Day 1 of Cycles 3, 5, 6, and 7:
  - Predose (within 2 hours prior to dosing)
- Every scheduled or unscheduled tumour assessment scan (if on day of infusion, collect pre- infusion)
- Disease progression/End of treatment - if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

17.9.3 Whole Blood Samples for [redacted]

Mandatory whole blood samples will be collected from all patients at the timepoints indicated below. [redacted] Note: Collection time begins with the start of the infusion.

Part A

- Screening
- Cycle 1, Weeks 1 and 3:
  - Predose (within 2 hours prior to dosing)
- Cycle 2, Days 1 and 15:
  - Predose (within 2 hours prior to dosing)
- Day 1 of Cycles 3, 5, and 7:
  - Predose (within 2 hours prior to dosing)
- Every scheduled or unscheduled tumour assessment scan (if on day of infusion, collect pre-infusion)
- Disease progression/End of treatment - if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

Part B

- Screening
- Cycle 1, Week 1:
  - Predose (within 2 hours prior to dosing)
- Cycle 1, Week 3:
  - Predose (within 2 hours prior to dosing)
  - 24 hours (± 2 hours) after the start of the infusion (and prior to acalabrutinib dosing)
- Cycle 2, Days 1 and 15:
  - Predose (within 2 hours prior to dosing)
- Day 1 of Cycles 3, 5, and 7
  - Predose (within 2 hours prior to dosing)
- Every scheduled or unscheduled tumour assessment scan (if on day of infusion, collect pre-infusion)

- Disease progression/End of treatment - if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

17.9.4 Whole Blood Samples for [redacted] (Part A and B)

Mandatory whole blood samples will be collected from all patients at the timepoints indicated below. [redacted] Note: Collection time begins with the start of the infusion.

Part A

- Screening
- Cycle 1, Week 1:
  - Predose (within 2 hours prior to dosing)
- Cycle 1, Week 3
  - Predose (within 2 hours prior to dosing)
- Cycle 2, Days 1 and 15:
  - Predose (within 2 hours prior to dosing)
- Every scheduled or unscheduled tumour assessment scan (if on day of infusion, collect pre-infusion)
- Disease progression/End of treatment - if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

Part B

- Screening
- Cycle 1, Week 1:
  - Predose (within 2 hours prior to dosing)
- Cycle 1, Week 3
  - Predose (within 2 hours prior to dosing)
- Cycle 2, Days 1 and 15
  - Predose (within 2 hours prior to dosing)
- Every scheduled or unscheduled tumour assessment scan (if on day of infusion, collect pre-infusion)
- Disease progression/End of treatment - if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

17.9.5 Whole Blood for [redacted] Exploratory Analysis (Part B Only)

Mandatory whole blood samples will be collected from all patients in [redacted] at the timepoints indicated below to analyse [redacted] Note: Collection time begins with the start of the infusion.

- Screening
- Cycle 1, Week 1:
  - Predose (within 2 hours prior to dosing)
- Day 1 of Cycles 2, 3, 5, and 7
  - Predose (within 2 hours prior to dosing)
- Every scheduled or unscheduled tumour assessment scan (if on day of infusion, collect pre-infusion)
- Disease progression/End of treatment - if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

17.9.6 Exploratory Blood [redacted] Samples

Mandatory whole blood samples will be collected in [redacted] from all patients at the timepoints indicated below. [redacted] Note: Collection time begins with the start of the infusion (see Section 10.2).

Part A and Part B

- Screening
- Cycle 1, Weeks 1 through 3 (AZD4573 first and second ramp-up and target dose and target dose):
  - Predose (within 2 hours prior to dosing)
  - 2 hours (± 15 minutes) after the start of the infusion
  - 24 hours (± 2 hours) after the start of the infusion (and prior to acalabrutinib dosing)
- Day 1 of Cycles 2, 3, 5, and 7:
  - Predose (within 2 hours prior to dosing)
- Every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion)

- Disease progression/End of treatment - if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

Further details on sample processing, handling, and shipment are provided in the Laboratory Manual.

17.10 CCI

CCI

17.10.1 Collection of Archival Tumour Samples

All patients in Part A (dose setting) must consent to and provide a sample of their archival tumour obtained within 24 months before the first dose of treatment. The archival tumour biopsy sample formalin-fixed paraffin embedded (FFPE) tumour block should be provided with sufficient material to produce 20 slides, or where an archival tumour biopsy FFPE tumour block is unavailable, archival tumour biopsy FFPE unstained slides (20 unstained slides preferable, minimum 15 slides acceptable) must be provided. Archival tissues must have been obtained as a core biopsy and meet the specified criteria detailed in the Laboratory Manual. Associated pathology report(s) for archival tissue samples must be obtained at Screening for all patients enrolled into the study.

If archival material is unavailable or unsuitable for use, patients must consent to and undergo a tumour biopsy during the screening period. A new biopsy is strongly encouraged and preferred over an archival sample (see Section 17.10.2) as these samples will be used to confirm cell of origin status and to determine additional DLBCL subtyping. A patient will be enrolled based on a prior pathology report.

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

17.10.2 Collection of Tumour Biopsy Samples

Patients in Part A who are unable to provide archival tumour specimens obtained within 24 months before the first dose of treatment will be asked to undergo a tumour biopsy at Screening. A new biopsy is strongly encouraged and preferred over an archival sample.

All patients in Part B (Phase II cohort expansions) will be asked to provide a newly obtained tumour biopsy at Screening. This sample will be used to confirm cell of origin

status, determine additional DLBCL subtype, and evaluate potential patient selection biomarkers through methods such as, but not limited to, immunohistochemistry (eg, baseline expression of Bfl1), gene expression analysis, and DNA sequencing. A patient will not be enrolled into Part B if he/she is unable to provide a newly obtained or recent biopsy. A recent biopsy that was taken as part of SoC prior to screening consent for this study is acceptable if no treatment was administered between the biopsy and the first dose of study treatment, and the biopsy was taken within 60 days prior to receiving the first dose.

All patients are also encouraged to consent to an additional optional tumour biopsy at disease progression. The optional disease progression sample may be taken at the 30-day SFU visit if not collected previously (see Section 17.10.5).

The tumour biopsy procedure will be performed by core needle, under radiological guidance, or surgically if the site of disease is superficial and palpable or visible (eg, palpable lymph node). Tumour biopsies should be preferentially obtained from tumour tissues that are safely accessible, as determined by the Investigator, and are not obtained from sites that require significant risk procedures. Patients will undergo 6 core image-guided needle biopsies. It is mandated that the core biopsy be removed directly from the tumour in situ and not cored from a surgically removed tumour. This is to ensure the best possible quality of the biopsy, as the blood/nutrient supply to the tumour is not disrupted prior to biopsy collection. Fine-needle aspirate specimens are not acceptable. Failure to obtain sufficient tumour sample after making best efforts to biopsy the tumour will not be considered a protocol deviation.

Sites should confirm the adequacy of tumour biopsy material at the time of the procedure. The exact time that the biopsy was taken should be clearly noted in the associated documentation. For mandatory and optional biopsy patients, the associated pathology report(s) for fresh tumour samples will be required at Screening and requested on treatment for all patients enrolled into the study.

Further details on sample processing, handling, and shipment are provided in the Laboratory Manual.

17.10.3 Collection of Bone Marrow

For all patients, when bone marrow biopsy and aspirate samples are collected for local standard disease profiling (refer to Section 17.4.3 for timepoints), CCI [redacted]

CCI [redacted]

Instructions on sample collection, labelling, processing, storage, and shipping will be provided in the laboratory manual.

17.10.4 Other Study Related [redacted] Research

17.10.4.1 [redacted] Sample for [redacted] Isolation

[redacted]

The sample should be collected from patients before receiving study treatment (Cycle 1, Week 1: Predose).

Details on sample processing, handling, and shipment are provided in the Laboratory Manual.

17.10.5 Collection of Optional [redacted] Samples

Collection of optional samples for [redacted] research is also part of this study as specified in the SoA (Section 10.2) and is subject to agreement to optional consent.

17.10.5.1 Optional Tumour Biopsy at Disease Progression

For patients who consent to the optional tumour biopsy, a biopsy will be taken at disease progression. The disease progression sample may be taken at the SFU visit if not collected previously.

Details on sample processing, handling, shipment, and storage are provided in the Laboratory Manual.

17.11 Optional Genomics Initiative Sample

Collection of optional saliva samples for genomics initiative research is also part of this study as specified in the SoA (Section 10.2) and is subject to agreement in the ICF addendum.

A saliva sample for DNA isolation will be collected from patients who have consented to participate in the genetic analysis component of the study. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study.

The saliva sample for exploratory genetic research will be obtained from the patients before the first dose of IP. If for any reason the sample is not taken before dosing it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

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

For storage and destruction of genetic samples, please refer to Appendix D.

17.12 Medical Resource Utilisation and Health Economics

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

17.13 Important Medical Procedures to be Followed by the Investigator

17.13.1 Medical Emergencies and Contacts

The principal Investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, please refer to Section 8.2.10.**

In the case of a medical emergency the Investigator may contact the Medical Monitor. If the Medical Monitor is not available, contact the Medical Scientist.

18 STATISTICAL CONSIDERATIONS – MODULE 1

18.1 Statistical Hypotheses

No hypotheses are planned to be tested.

18.2 Sample Size Determination

Depending on dose escalation/de-escalation and enrolment in the expansion groups, up to a maximum of 105 evaluable patients will be treated with AZD4573 + acalabrutinib in this module.

The primary objective of Part A (dose setting) will be to identify the MTD and/or RP2D. In Part A, 3 to 9 evaluable patients may be treated in each of up to 3 dose levels using an mTPI-2 design permitting up to a maximum of 24 DLT-evaluable patients for dose setting (ie, a maximum of 9 evaluable patients at each of two dose levels and 6 evaluable patients at the third dose level). In addition, any safe dose level may be backfilled to include up to approximately 21 evaluable patients to collect additional tolerability and exploratory data. The maximum number of evaluable patients in Part A is therefore 63. This limits the number of patients exposed consistent with the expected safety profiles of the study drugs, but includes sufficient patients to explore safety of the combination treatment, PK, and effects on pharmacodynamic biomarkers, and to collect preliminary efficacy data.

In Part B (expansion), separate RP2D expansion cohorts will be opened for GCB and non-GCB DLBCL subtypes. For primary analyses, approximately 21 RP2D treated response evaluable patients of GCB subtype and approximately 21 RP2D-treated response-evaluable patients of non-GCB subtype will be incorporated, including patients from Part A and Part B. The total number of evaluable patients treated in Part B will be up to approximately 42. This sample size is large enough to evaluate further the safety and pharmacokinetics/pharmacodynamics (PKPD) of the chosen dose/schedule for AZD4573 + acalabrutinib from Part A and gives a reasonable chance of detecting an efficacy signal.

Historical response rates in r/r DLBCL are in the region of 30% to 60%, with some evidence that response rates are higher for the non-GCB subtype (Hernandez-Ilizaliturri et al 2011, Morschhauser et al 2014, Van den Neste et al 2016, Van den Neste et al 2017, Wang et al 2018, Wang et al 2020, Wilson et al 2015, Witzig et al 2011). The following examples give an indication of the level of precision that will be achieved in this study:

- CCI [redacted]

- CCI [redacted]
- CCI [redacted]

In addition to ORR, the criteria for success will take into account the observed safety and tolerability data, and the other efficacy endpoints, in particular the DoR.

The data cut-off for the primary analysis for each expansion subgroup will occur approximately 6 months following last patient first dose in the expansion subgroup or when 75% of patients have progressed or died in the cohort, whichever occurs first.

Treatment with AZD4573 and acalabrutinib, in Part A and Part B, may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol, or the patient withdraws or is withdrawn from the study for other reasons. Patients who discontinue both study drugs before documented disease progression will be followed according to SoC until documented disease progression or the start of new anti-cancer therapy. All patients will be followed for survival until death, loss to follow-up, AstraZeneca closes study or withdrawal of consent, whichever occurs first.

18.3 Populations for Analyses

The analysis of data will be based on different subsets according to the purpose of the analysis.

Analysis sets are presented in Table 22.

Table 22 Analysis Sets

Analysis Set	Definition
Enrolled	All participants who sign the ICF
Safety	All patients who received any amount of AZD4573 and/or acalabrutinib.
DLT-evaluable	Patients that have received AZD4573 in combination with acalabrutinib and either: • Have received at least 3 doses of AZD4573 at the designated target dose level, have received at least 75% of acalabrutinib doses, and have completed the SFU through the DLT-assessment period. Or • Have experienced a DLT

Analysis Set	Definition
Pharmacokinetics	All dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK.
Response evaluable	Patients dosed with AZD4573 or acalabrutinib with a baseline tumour assessment.
Interim response evaluable	Participants 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
FAS/ITT	All participants who received any amount of study intervention

Abbreviations: DLT = dose-limiting toxicity; ICF = informed consent form; FAS=Full analysis set; ITT = intent-to-treat; PK = pharmacokinetics.

18.4 Statistical Analyses

The Statistical Analysis Plan (SAP) will be finalised prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints, as defined in Section 3 (Table 7).

18.4.1 General Considerations

Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and CIs for discrete variables) will be used to summarise data by dose level/cohort as appropriate. KM methods will be used to estimate DoR, PFS and OS; corresponding quartiles (including the median) and 6-month and 12-month rates may be presented as appropriate.

18.4.2 Demographics, Baseline Characteristics, and Study Status

Characteristics of the participants, including medical history, disease characteristics at baseline, and previous and concomitant treatments (coded according to WHODRUG) will be listed for each participant and summarised by dose level/cohort where appropriate.

Reasons for discontinuation of study treatment and withdrawal from study will be listed including the study day of treatment discontinuation/study withdrawal and will be summarised by dose level/cohort if appropriate.

18.4.3 Exposure

Exposure to AZD4573 and acalabrutinib will be listed for all participants.

Exposure amounts, durations, and dose modifications and interruptions/delays will be summarised by study drug, separately for Cycle 1 (including intra-patient ramp up) and for other treatment cycles.

18.4.4 Safety

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs, and ECG changes.

For Part A, where safety is the primary objective, DLTs will be listed and summarised; MTD (if determined) will be reported. For both study parts, appropriate listings and summaries of all safety data will be produced, as defined below.

Adverse events will be listed individually by participant and dose level/cohort. The number of participants experiencing each AE will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade, with the exception of TLS which will use both CTCAE grade and Howard modification of Cairo-Bishop criteria (see Appendix F). The number and percentage of participants with AEs in different categories (eg, causally related and CTCAE Grade ≥ 3) will be summarised by dose level/cohort, and events in each category will be further summarised by MedDRA system organ class and preferred term. SAEs will be summarised separately if a sufficient number occur.

AE summary tables will include only treatment-emergent AEs. AEs will be defined as treatment-emergent if they have an onset or worsen (by Investigator report of a change in intensity/severity), during the study treatment until 30 days from the last dose of any study intervention, but prior to subsequent cancer therapy. AEs occurring outside this period will be flagged in listings.

Haematology, clinical chemistry, vital signs, ECG data, and other laboratory values will be listed individually by participant and suitably summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated.

Details of any deaths will be listed for all participants.

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

Depending on the extent of any impact, summaries of data relating to participants diagnosed with COVID-19, and impact of COVID-19 on the study conduct (for example,

missed visits, delayed or discontinued IP, and other protocol deviations) may be generated. More detail will be provided in the SAP.

ECG Changes

QTc will be calculated using Fridericia's formula.

Creatinine Clearance

Estimated creatinine clearance will be calculated using the Cockcroft and Gault formula.

Other Significant Adverse Events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation of study treatment. Based on the expert's judgement, AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the CSR. A similar review of laboratory values, vital signs, ECGs, and other safety assessments will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

18.4.5 Efficacy

Tumour response data will be listed and summarised by dose level/cohort, if appropriate, using the standard response criteria as defined in Section 17.4.

For GCB and non-GCB RP2D expansion cohorts, the primary endpoint is ORR; other efficacy endpoints are secondary. For Part A participants who are not included in the GCB and non-GCB RP2D expansion cohorts, all efficacy endpoints are exploratory.

18.4.5.1 Objective Response Rate and Proportion of Participants with Complete Response

Objective Response (OR) is defined as a best overall response of CR or PR that occurs prior to the initiation of subsequent anti-cancer treatment and prior to progression, or last evaluable assessment in the absence of progression. Objective Response Rate (ORR) is defined as the percentage of subjects with objective response (Cheson et al 2014). ORR and complete response rate (CRR) will be presented with corresponding 80% and 95% two-sided CIs.

18.4.5.2 Time to Response (TTR)

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 participants who achieved an objective response.

18.4.5.3 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. KM curves and estimates may be presented, if appropriate.

18.4.5.4 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 participant withdraws from therapy or receives another anti-cancer therapy prior to progression. Participants who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable disease assessment. However, if the participant progresses or dies immediately after 2 or more consecutive missed visits, the participant is censored at the time of the latest evaluable disease assessment prior to the 2 missed visits.

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

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

- Date of progression will be determined, based on the earliest of the dates of the component that triggered the progression.
- When censoring a participant for PFS, the participant will be censored at the latest of the dates contributing to a particular overall visit assessment.

Kaplan-Meier plots will be provided.

18.4.5.5 Overall Survival (OS)

OS is defined as the time from first dose until the date of death from any cause. Participants 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. Participants known to be alive or dead after the data cut-off date will be censored at the data cut-off date. Participants who are lost to follow-up will be censored at the date the participant is last known to have been alive. KM curves and estimates may be presented, if appropriate.

18.4.6 Pharmacokinetics

Pharmacokinetics is a secondary objective for Part A and Part B.

Plasma concentrations of AZD4573 plus acalabrutinib and its metabolite ACP-5862 will be summarised by nominal sample time. Plasma concentrations and derived PK parameters will be summarised by cohort and dose level. Plasma concentrations and the derived PK parameters at each time point will be summarised according to dose level/cohort by the following summary statistics:

- The geometric mean (gmean)
- Coefficient of variation (CV)
- Gmean ± standard deviation
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum
- Median
- Maximum
- Number of observations

The pharmacokinetic data for AZD4573, acalabrutinib and its metabolite ACP-5862 will also be displayed graphically. Displays will include plasma concentration participant profiles (on the linear and log-scale) versus time and gmean concentration (± standard deviation) versus time, stratified by dose.

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

Derived PK parameters to be determined include Cmax, AUC0-t, AUClast, AUC0-inf, tmax, and t1/2. Additional PK parameters may be determined.

18.5 Interim Analyses

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

18.6 Safety Review Committee – Module 1

An SRC, which includes the principal investigators, is tasked with the review of the available safety data (AEs and available pharmacokinetics/pharmacodynamics [PKPD] data) for AZD4573 in combination with acalabrutinib prior to the SRC making

recommendations on opening next cohorts or changing the dose schedule. All decisions are and will be documented in writing in the form of meeting minutes.

Please refer to Appendix A 5 and the SRC Charter for further information on the SRC.

In Part A, once all participants in a given dose setting cohort have had the opportunity to become DLT-evaluable, the SRC will review and assess all available safety data, together with available PK data, to make a decision on the dose for the subsequent combination therapy cohort of participants. At least 3 evaluable participants are required before a dose-escalation decision can be made. Any dose interruptions and reductions will be taken into account.

The decision (guided by mTPI-2) may be to:

1 Proceed with dose escalation for the next cohort, up to a maximum of 9 evaluable participants per dose level.
2 Treat the next cohort at the same level, up to a maximum of 9 evaluable participants at any one dose level.
3 De-escalate the dose for the next cohort, up to a maximum of 9 evaluable participants at the lower dose level.
4 Stop the dose-escalation part of the study.
5 Evaluate alternative/intermittent dose schedules or change dosing to weight-based or body surface-area based dosing.

Additionally, as described in Section 15.2, beyond the dose setting phase Part A and Part B participants, including backfills, receiving the RP2D of AZD4573 + acalabrutinib combination therapy will be monitored for any DLTs and for TLS events resulting in study treatment discontinuations using the same DLT criteria employed during dose setting. If, on an ongoing basis, > 30% of participants experience any safety events that meet the criteria of a DLT or > 30% of participants discontinue study treatment due to TLS, enrolment into the expansion cohorts may be paused for evaluation of the study data by the SRC. Following SRC review additional monitoring may be implemented and/or enrolment and dosing may resume at a lower combination dose level or modified schedule as defined in the dose setting phase. Further details will be provided in the Medical Monitoring Plan.

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

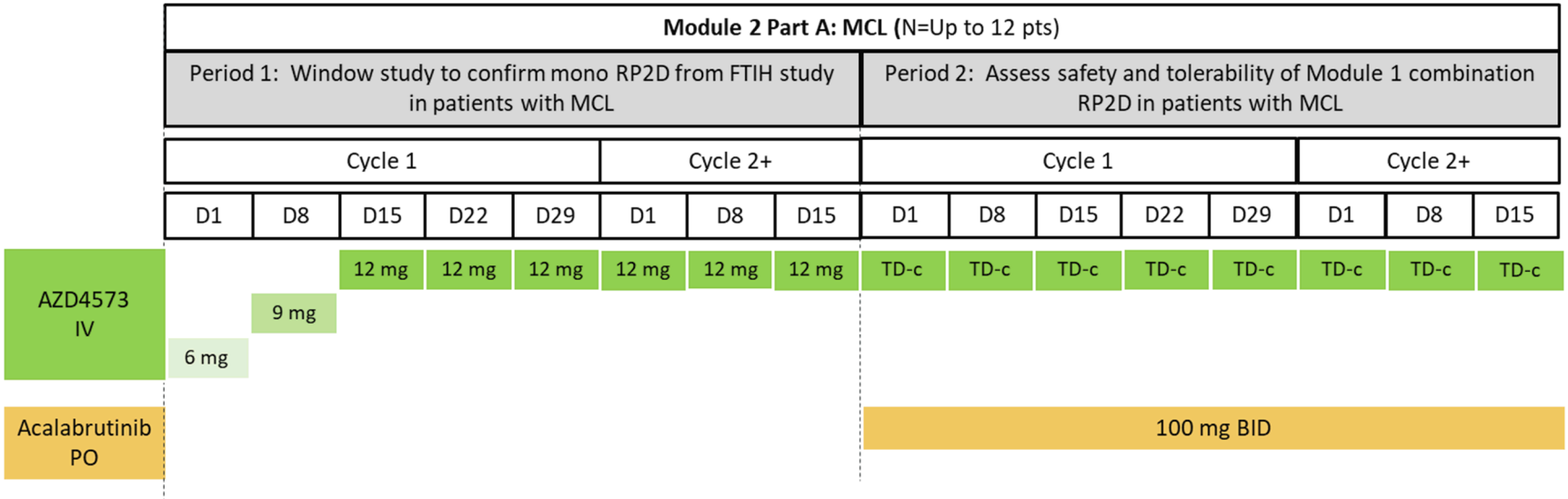
The decisions and decision-making of the SRC on the next dose level will be documented and provided to the investigators before dosing any new participants.

MODULE 2: AZD4573 MONOTHERAPY WINDOW STUDY FOLLOWED BY AZD4573 PLUS ACALABRUTINIB IN PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA

19 PROTOCOL SUMMARY – MODULE 2

19.1 Scheme

Figure 6 **Overall Study Design for AZD4573 Monotherapy Window Study Followed by AZD4573 Plus Acalabrutinib in Participants with Relapsed or Refractory Mantle Cell Lymphoma – Module 2, Part A**



Notes: FTIH study = D8230c00001. All participants will start on AZD4573 monotherapy (Period 1) and will thereafter follow the schedule in Table 29.
Abbreviations: BID = twice a day; PO = by mouth; IV = intravenous; MCL = mantle cell lymphoma; TD-c = target dose for combination recommended Phase 2 dose.

There is a SoA for each Period of Part A (Table 23 and Table 24).

The study design of Part B of this module will be determined from the data emerging from Part A. Specifics for Part B will be defined in a future protocol amendment.

19.2 Schedules of Activities – Module 2

Table 23 Schedule of Activities: (AZD4573 Monotherapy) Module 2, Part A, Period 1

Assessment	Screen[a]	Period 1 AZD4573 Monotherapy									Disease Assessment[b] /End of Treatment[kk]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1 - 5					Cycles 2-8 (Cycle = 21 days)			Cycles 9+ (Cycle = 21 days)[ii]				
		Days					Days			Day				
		1	8	15	22	29	1	8	15	1				
		(±2 Days)					(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Informed consent[d]	X													Section 26.1.1
Inclusion/exclusion	X													Section 26.1.1
Medical history and demographics	X													Section 26.1.1
Physical examination[f]	X	X	X	X	X	X	X	X	X	X		X		Section 26.1.2
ECOG performance status	X	X	X	X	X	X	X	X	X	X		X		Section 26.1.5
Archival tumour sample or new biopsy	X													Section 26.10.1, 26.10.2
Vital signs[e]	X	X	X	X	X	X	X	X	X	X (each infusion)		X		Section 26.1.3
Weight[f]	X	X					X			X		X		Section 26.1.3
B symptoms	X	X	X	X	X	X	X	X	X	X		X		Section 26.1.6

Assessment	Screen[a]	Period 1 AZD4573 Monotherapy									Disease Assessment[b] /End of Treatment[kk]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1 - 5					Cycles 2-8 (Cycle = 21 days)			Cycles 9+ (Cycle = 21 days)[ii]				
		Days					Days			Day				
		1	8	15	22	29	1	8	15	1				
		(±2 Days)					(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
12-lead ECG[g]	X	X	X	X	X	X	X			X		X		Section 26.1.4
CMV immunoglobulin M [IgM] and PCR[h]	X													Section 26.1.7
Cardiac troponin[i]	X	X	X	X	X	X	X			X		X		Section 26.1.7
T4, cortisol, ACTH and TSH[j]	X						Cycle 2 only					X		Section 26.1.7
ECHO/MUGA[k]	X	As clinically indicated										X[k]		Section 26.1.8
Haematology[l]	X	X	X	X	X	X	X	X	X	X (each infusion)		X		Section 26.1.7
Coagulation[m]	X	X	X	X	X	X	X	X	X	X		X		Section 26.1.7
Clinical chemistry[n]	X	X	X	X	X	X	X	X	X	X (each infusion)		X		Section 26.1.7
TLS monitoring[o]		X	X	X										Section 26.1.7
Urinalysis[p]	X	X	X	X	X	X	X	X	X	X		X		Section 26.1.7

Assessment	Screen[a]	Period 1 AZD4573 Monotherapy									Disease Assessment[b] /End of Treatment[kk]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1 - 5					Cycles 2-8 (Cycle = 21 days)			Cycles 9+ (Cycle = 21 days)[ii]				
		Days					Days			Day				
		1	8	15	22	29	1	8	15	1				
		(±2 Days)					(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Pregnancy testing (women of childbearing potential)[q]	X (Serum)	X	Once every 21 days									X		Section 26.1.7
Lipase/amylase[r]	X	X	X	X	X	X	X	X	X	X		X		Section 26.1.7
Hepatitis serology[s]	X						See footnote							Section 26.1.7 and Section 26.1.10.4
CD4, CD8, CD19, CD16/NK cell count[t]	X						X (predose)[t]	Every 6 months				X		Section 26.1.8
Serum immunoglobulins (IgA, IgM, IgG)[t]	X						X (predose)[t]	Every 6 months				X		Section 26.1.8
Concomitant medication	X	X	X	X	X	X	X	X	X	X (each infusion)	X	X	X	Section 24.8
Adverse event evaluation	X	X	X	X	X	X	X	X	X	X (each infusion)	X	X	X	Section 8.2
AZD4573 plasma PK[u]		X	X	X			Cycle 2							Section 26.6

Assessment	Screen[a]	Period 1 AZD4573 Monotherapy: Cycle 1 Weeks 1 - 5 Days 1	8	15	22	29	Cycles 2-8 (Cycle = 21 days) Days 1	8	15	Cycles 9+ (Cycle = 21 days)[ii] Day 1	Disease Assessment[b] /End of Treatment[kk]	30-Day SFU[c]	LTFU	Details in CSP Section
		(±2 Days)					(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Pharmacodynamic samples (blood) for AZD4573[v]		X	X	X										Section 26.7.1
CCI	X	X	X	X	CCI									Section 26.8
Whole blood for exploratory CCI [x]	X	X		X		X	Cycles 2, 3, 5, 6, and 7		Cycle 2		X	(X)		Section 26.9.1
Whole Blood for CCI [y]	X	X		X		X	Cycles 2, 3, 5, 6, and 7		Cycle 2		X	(X)		Section 26.9.2
Whole blood samples for CCI [z]	X	X		X			Cycles 2, 3, 5, and 7		Cycle 2		X	(X)		Section 26.9.3
Whole blood samples for CCI [aa]	X	X		X			Cycle 2		Cycle 2		X	(X)		Section 26.9.4
Whole blood for CCI exploratory analysis[bb]	X	X					Cycles 2, 3, 5, and 7				X	(X)		Section 26.9.5
Exploratory blood CCI [cc]	X	X	X	X			Cycles 2, 3, 5, ad 7				X	(X)		Section 26.9.6

Assessment	Screen[a]	Period 1 AZD4573 Monotherapy									Disease Assessment[b] /End of Treatment[kk]	30-Day SFU[c]	LTFU	Details in CSP Section
		Cycle 1 Weeks 1 - 5					Cycles 2-8 (Cycle = 21 days)			Cycles 9+ (Cycle = 21 days)[ii]				
		Days					Days			Day				
		1	8	15	22	29	1	8	15	1				
		(±2 Days)					(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
CCI sample for CCI isolation[dd]	(X)	X (pre-dose)												Section 26.10.4.1
Genomics Initiative saliva sample (**optional**)[ee]	(X)	X (pre-dose)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		Section 26.11
Tumour biopsy sample (**optional**)[ff]											At disease progression	(X)[ff]		Section 26.10.2
Bone marrow biopsy & aspirate[gg]	X										As clinically indicated and to confirm CR			Section 26.4.3 and Section 26.10.3
Disease assessment[b] and radiologic scans[hh]	X	See Table 37 schedule										X		Section 26.4.2
AZD4573 intravenous[ii]		Once weekly (from Cycle 1, Week 1 to end of treatment)[ll]												Section 24.1
Disease progression follow-up (SoC)													X	Section 26.1.9.2
Survival Follow-up													X	Section 26.1.9.3

[a] Screening tests should be performed within 30 days before the first administration of study drug, unless otherwise indicated.

[b] Disease assessments will be done by the Investigator using the Lugano Response Criteria for Non-Hodgkin's Lymphoma (Cheson et al 2014). Additional disease assessments may be performed as clinically indicated.

[c] The SFU visit will be performed 30 days (±7 days) after the last dose of all study drug. Tumour assessments will be repeated at this visit if they have not been performed within 9 weeks if the participant discontinued before or during Week 26, or 12 weeks if the participant discontinued after Week 26.

[d] Informed consent must be obtained ≤ 30 days before the first dose of study drug and must be obtained before any protocol-defined screening procedures are done.

[e] Vital signs (blood pressure, pulse rate, temperature) will be assessed after the participant has rested for at least 10 mins. Blood pressure and pulse rate will be measured at Screening, and on Day 1 of Cycle 1, Weeks 1-3 at the following timepoints: predose (within 2 h prior to infusion), 1 h after the start of the infusion (± 10 mins), at end of infusion (up to 10 mins post dose) and then 4 h (± 30 mins) and 6 h (± 30 mins) after start of infusion, from Cycle 1 Week 4 onwards, at predose (up to 30 mins prior to infusion), at the end of infusion (up to 30 mins post dose), and at the 30-day SFU. Temperature to be taken pre-infusion (up to 2 h prior to all infusions).

[f] As the study is intended to recruit adults, height should only be measured at Screening. Weight to be measured at Screening, prior to infusion on Day 1 of each cycle, and at the 30-day SFU visit.

[g] Participants should be in semi-supine position and resting for ≥ 10 mins before the ECGs. Single ECGs for local and central analysis are required at Screening and at the following timepoints: for Cycle 1, Weeks 1-5 and Cycle 2 Day 1 predose (at the day of infusion prior to infusion) and within 30 mins of the end of infusion; for Cycles 3+ on Day 1 within 30 mins after the end of infusion, and at the 30-day SFU visit.

[h] All subjects will have CMV testing at Screening including serology testing for CMV immunoglobulin (Ig)G and CMV IgM and CMV DNA PCR testing

[i] Cardiac troponin measurements are required at the following timepoints: Screening, Cycle 1, Weeks 1-5, predose (within 72 hours prior to infusion) and at 24 h after the start of the infusion, and Cycles 2+ on Day 1 of each cycle, predose (within 72 hours prior to infusion), and at the 30-day SFU visit. Note: either a troponin I or troponin T assay can be used per SoC at the respective hospital. If the hospital has both a SoC troponin I and troponin T assay available, the investigator shall use only one consistently for the duration of the study.

[j] T4, cortisol, ACTH, and TSH to be taken at Screening, predose (within 72 hours prior to infusion) on Cycle 2, Day 1, and at the 30-day SFU.

[k] ECHO should be done at Screening and within 14 days after an abnormal ECG finding (eg, T-wave inversion/flattening) or as soon as possible when clinically indicated. If an ECHO cannot be taken, a MUGA scan to assess LVEF will be done. In case of any T-wave abnormality, the ECHO (or MUGA) should be repeated at the 30-day follow-up visit to address the question of recovery, during the off-treatment period.

[l] Haematology testing should be measured at Screening, Cycles 1, 2, and 3 predose (within 72 h prior to infusion) and 24 h after the start of the infusion. From Cycle 4 onwards, haematology testing should be predose (within 72 h prior to infusion) and (if clinically indicated) 24 h after the start of the infusion. A sample will also be drawn at the 30-day SFU. The Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF. Haematology tests do not need to be repeated before first dose if the first-dose visit is within 3 days of the Screening sample.

[m] Coagulation testing should be measured at Screening, Cycles 1, 2, and 3 predose (within 72 h prior to infusion) and 24 h post-infusion of AZD4573. For Cycles 4-8, predose (within 72 h prior to the infusion); the 24-h sample can be omitted unless clinically indicated. For Cycles 9+, on Day 1 of each cycle, an AZD4573 pre-infusion sample will be drawn within 72 h prior to infusion. A sample will also be drawn at the 30-day SFU. The Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF.

[n] Clinical chemistry should be measured at Screening, Cycles 1, 2, and 3 predose (within 72 h prior to infusion), and 24 h post-infusion of AZD4573. From Cycle 4 onwards, clinical chemistry testing should be measured predose (within 72 h prior to infusion) and (if clinically indicated) 24 h after the start of the infusion.A sample will also be drawn at the 30-day SFU. The investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF. Clinical chemistry tests do not need to be repeated before first dose if the first-dose visit is within 3 days of the Screening sample.
In addition, GLDH and CPK will be measured at Screening for all participants. If GLDH cannot be performed locally, LDH will be analysed locally and a serum sample must be collected for central retrospective GLDH analysis, which will be performed as applicable. Refer to the Laboratory Manual for details.
If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, potassium) and troponin must be done to coincide with the ECG testing.

[o] All participants will receive TLS prophylaxis during the intra-patient ramp up and be monitored for TLS during the first 24 hours post start of dose; this requirement will continue until they have received at least one AZD4573 dose at the target dose level (i.e., for at least the first 3 AZD4573 once-weekly doses). TLS monitoring will be performed at the following timepoints: Cycle 1, Weeks 1-3, predose AZD4573, 6 h after the start of the infusion, and 24 h (± 1 h) after the start of the infusion. Participants showing signs of clinical or laboratory TLS at 6 h after start of infusion must be admitted for in-patient TLS monitoring for a minimum of 24 h after the start of the infusion and monitored every 4 to 6 h during this time (or more frequently if clinically indicated). For each TLS monitoring timepoint, a TLS Monitoring page in the eCRF is to be filled out. Fluid balance must be monitored according to local institutional standards.

[p] Urine samples will be collected at the following timepoints: Screening, Cycles 1-8, predose AZD4573 (within 72 hours prior to infusion) and within approximately 2 hours after the end of infusion, Cycles 9+ on Day 1 of each cycle, predose AZD4573 and within approximately 2 hours after the end of infusion, and at the 30-day SFU.

[q] Pregnancy test to be performed at Screening (serum) and predose (serum or urine) on Cycle 1, Week 1, then once every 21 days (± 7 days) prior to initiating a new cycle and at the 30-day SFU visit. Additional testing may be performed at Investigator discretion (eg, in the event of suspected contraception failure).

[r] Lipase and amylase should be evaluated at Screening, Cycles 1-8 predose AZD4573 (within 72 hours prior to infusion), Cycles 9+, predose AZD4573 (within 72 hours prior to infusion) on Day 1 of each cycle, and at the 30-day SFU visit.

[s] In addition to hepatitis serology as specified, participants who are anti-HBc positive, or have a known history of HBV infection, should be monitored every 3 months with a quantitative PCR test for HBV DNA. In addition, any participants testing positive for any hepatitis serology must have PCR testing for verification purposes.

[t] CD4, CD8, CD19, CD16/NK and serum immunoglobulins (IgA, IgM, IgG) will be drawn at Screening, Day 1 (predose) of Cycles 2, 4, 7, 9, 13, 16, 19 and every 6 months thereafter (predose), and at the 30-day SFU.

[u] Plasma samples for PK analysis will be taken at the following time points: For Cycle 1, of Weeks 1-3 and Cycle 2, Day 1: predose (up to 2 h prior to AZD4573) and 1 h (± 15 mins), 2 h (± 15 mins), 4 h (± 30 mins), 7 h (± 1 h), and 24 h (± 1 h) (ie, Day 2 of dosing) after the start of the infusion.

[v] Pharmacodynamic evaluations for AZD4573 blood samples will be collected at Cycle 1, Weeks 1 and 2 at predose (up to 2 h prior to dosing) and 2 h (± 15 mins), 4 h (± 30 mins), and 24 h (± 2 h) (ie, Day 2) after the start of the infusion. Cycle 1 Week 3, predose (up to 2h prior to dosing), 2 h (± 15 mins), 4 h (± 30 mins), 7 h (± 1 h), and 24 h (± 2 h) (ie, Day 2) after the start of the infusion.

[w] CCI [redacted] Samples will be taken for all participants at Screening and Cycle 1, Weeks 1-3: predose (up to 2 h prior to dosing) and 4 h (± 30 mins), 7 h (± 1 h), and 24 h (± 1 h) after start of infusion. CCI [redacted] at 24 h after start of infusion, samples will be drawn at 48 h(-2 h/+12 h prior to infusion), 96 h (- 2 h/+12 h prior to infusion), predose-the-following infusion (within 4 h prior to infusion), and at each point chemistry panel testing is being performed. CCI [redacted] sampling should be performed the same as for Cycle 1, Weeks 1-3.

[x] Whole blood for exploratory CCI [redacted] samples will be collected at Screening, Cycle 1, Weeks 1, 3, and 5 predose (within 2 h prior to dosing), Cycle 2, Days 1 and 15 predose (within 2 h prior to dosing), Day 1 of Cycles 3, 5, 6 and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[y] Whole Blood for CCI [redacted] analysis will be collected at Screening, Cycle 1, Weeks 1, 3, and 5 predose (within 2 h prior to dosing), Cycle 2, Days 1 and 15, predose (within 2 h prior to dosing), and on Day 1 of Cycles 3, 5, 6, and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[z] Whole blood samples for CCI [redacted] will be collected at Screening, Cycle 1, Weeks 1 and 3 predose (within 2 h prior to dosing), Cycle 2, Days 1 and 15, predose (within 2 h prior to dosing), Day 1 of Cycles 3, 5, and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[aa] Whole blood samples for CCI will be collected at Screening, Cycle 1, Weeks 1 and 3 predose (within 2 h prior to dosing), Cycle 2, Days 1 and 15 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[bb] Whole blood for CCI exploratory analysis samples will be collected at, Cycle 1, Week 1 predose (within 2 h prior to dosing), Day 1 of Cycles 2, 3, 5, and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[cc] Exploratory blood CCI Whole blood samples will be collected at Screening and Cycle 1 Weeks 1-3 at predose (within 2 h prior to dosing), 2 h (± 15 mins) and 24 h (± 2 h) after the start of the infusion and on Day 1 of Cycles 2, 3, 5, and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[dd] CCI sample for CCI isolation will be collected at Cycle 1, Week 1 predose.

[ee] An optional saliva sample for genomics initiative research will be taken from consenting participants prior to the first dose of IP. If for any reason the sample is not taken before dosing it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

[ff] A biopsy will be taken at disease progression for participants who consent. The disease progression sample may be taken at the SFU visit if not collected previously.

[gg] Bone marrow biopsy and aspirate: CCI

[hh] See Table 37 for schedule of disease assessments, including mandatory PET assessments. Disease assessments will be done by the Investigator using the Lugano Response Criteria for Non-Hodgkin's Lymphoma (Cheson et al 2014). Additional disease assessments may be performed as clinically indicated.

[ii] AZD4573 is to be administered as an absolute (flat) dose, 2-h (± 15 mins) IV infusion on a once-weekly schedule.

[jj] If a participant is attending Cycle 9+ visits according to a modified schedule, in which AZD4573 is not infused and assessments are not performed every week, the Day 1 assessments should be performed at least once per cycle.

[kk] The End of Treatment visit is the last visit attended by the participant prior to the 30-Day SFU on the study. At this visit, the participant does not receive IMP and should undergo the applicable assessments associated with the Cycle and visit they have reached, plus those shown in the "Disease Assessment/End of Treatment" column of the SoA.

[ll] AZD4573 should be administered at least 5 days apart

Abbreviations: ACTH = adrenocorticotropic hormone; BID = twice daily; CPK = creatinine phosphokinase; CMV = cytomegalovirus; CSP = clinical study protocol; DNA = deoxyribonucleic acid; ECG = electrocardiogram, ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; GLDH = glutamic dehydrogenase; HBV = Hepatitis B virus; h = hour; Ig = immunoglobulin; IP = investigational product; CCI LTFU = long-term follow-up; LVEF = left ventricular ejection fraction; min = minutes; CCI MUGA = multigated acquisition; PCR = polymerase chain reaction; CCI PHL = Potential Hy's Law; PK = pharmacokinetics; SFU = safety follow-up; SoC = standard of care; T4 = thyroxine; TLS = tumour lysis syndrome; TSH = thyroid-stimulating hormone.

Table 24 Schedule of Activities: (AZD4573 + Acalabrutinib) – Module 2, Part A, Period 2

Assessment	Period 2 AZD4573 +Acalabrutinib									Disease Assessment[a] /End of Treatment[ii]	30-Day SFU[b]	LTFU	Details in CSP Section
	Cycle 1 Weeks 1 - 5					Cycles 2-8 (Cycle = 21 days)			Cycles 9+ (Cycle = 21 days)[hh]				
	Days					Days			Day				
	1	8	15	22	29	1	8	15	1				
	(±2 Days)					(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Physical examination[d]	X	X	X	X	X	X	X	X	X		X		Section 26.1.2
ECOG performance status	X	X	X	X	X	X	X	X	X		X		Section 26.1.5
Vital signs[c]	X	X	X	X	X	X	X	X	X (each infusion)		X		Section 26.1.3
Weight[d]	X					X			X		X		Section 26.1.3
B symptoms	X	X	X	X	X	X	X	X	X		X		Section 26.1.6
12-lead ECG[e]	X	X	X	X	X	X			X		X		Section 26.1.4
Cardiac troponin[f]	X	X	X	X	X	X			X		X		Section 26.1.7
T4, cortisol, ACTH and TSH[g]						X (Cycle 2 only)					X		Section 26.1.7
ECHO/MUGA[h]	As clinically indicated												Section 26.1.8
Haematology[i]	X	X	X	X	X	X	X	X	X (each infusion)		X		Section 26.1.7

Assessment	Period 2 AZD4573 +Acalabrutinib									Disease Assessment[a] /End of Treatment[ii]	30-Day SFU[b]	LTFU	Details in CSP Section
	Cycle 1 Weeks 1 - 5					Cycles 2-8 (Cycle = 21 days)			Cycles 9+ (Cycle = 21 days)[hh]				
	Days					Days			Day				
	1	8	15	22	29	1	8	15	1				
	(±2 Days)					(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Coagulation[j]	X	X	X	X	X	X	X	X	X		X		Section 26.1.7
Clinical chemistry[k]	X	X	X	X	X	X	X	X	X (each infusion)		X		Section 26.1.7
Urinalysis[l]	X	X	X	X	X	X	X	X	X		X		Section 26.1.7
Pregnancy testing (women of childbearing potential)[m]	Once every 21 days										X		Section 26.1.7
Lipase/amylase[n]	X	X	X	X	X	X	X	X	X		X		Section 26.1.7
Hepatitis serology[o]	See footnote												Section 26.1.7 and Section 26.1.10.4
CD4, CD8, CD19, CD16/NK cell count[p]						X (predose)[p]	Every 6 months				X		Section 26.1.8
Serum immunoglobulins (IgA, IgM, IgG)[p]						X (predose)[p]	Every 6 months				X		Section 26.1.8
Concomitant medication	X	X	X	X	X	X	X	X	X (each infusion)	X	X	X	Section 24.8

Assessment	Period 2 AZD4573 +Acalabrutinib									Disease Assessment[a] /End of Treatment[ii]	30-Day SFU[b]	LTFU	Details in CSP Section
	Cycle 1 Weeks 1 - 5					Cycles 2-8 (Cycle = 21 days)			Cycles 9+ (Cycle = 21 days)[hh]				
	Days					Days			Day				
	1	8	15	22	29	1	8	15	1				
	(±2 Days)					(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Adverse event evaluation	X	X	X	X	X	X	X	X	X (each infusion)	X	X	X	Section 8.2
AZD4573/ acalabrutinib plasma PK[q]	X		X										Section 26.6
Pharmacodynamic samples (blood) for AZD4573[r]	X												Section 26.7.1
Pharmacodynamic samples (blood) for acalabrutinib[s]	X			X									Section 26.7.1
CCI	X	CCI											Section 26.8
Whole blood for exploratory CCI [u]	X		X		X	Cycles 2, 3, 5, 6, and 7		Cycle 2		X	(X)		Section 26.9.1
Whole Blood for CCI [v]	X		X		X	Cycles 2, 3, 5, 6, and 7		Cycle 2		X	(X)		Section 26.9.2
Whole blood samples for CCI [w]	X		X			Cycles 2, 3, 5, and 7		Cycle 2		X	(X)		Section 26.9.3
Whole blood samples for CCI [x]	X		X			Cycle 2		Cycle 2		X	(X)		Section 26.9.4
Whole blood for CCI exploratory analysis[y]	X					Cycles 2, 3, 5, and 7				X	(X)		Section 26.9.5

Assessment	Period 2 AZD4573 +Acalabrutinib									Disease Assessment[a] /End of Treatment[ii]	30-Day SFU[b]	LTFU	Details in CSP Section
	Cycle 1 Weeks 1 - 5					Cycles 2-8 (Cycle = 21 days)			Cycles 9+ (Cycle = 21 days)[hh]				
	Days					Days			Day				
	1	8	15	22	29	1	8	15	1				
	(±2 Days)					(±2 Days)			(-2 to +5 Days)	(±7 Days)	(±7 Days)		
Exploratory blood [CCI redacted][z]	X					Cycles 2, 3, 5, and 7				X	(X)		Section 26.9.6
Genomics Initiative saliva sample (**optional**)[aa]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		Section 26.11
Tumour biopsy sample (**optional**)[bb]										At disease progression	(X)		Section 26.10.2
Bone marrow biopsy & aspirate[cc]										As clinically indicated and to confirm CR			Section 26.4.3and Section 26.10.3
Disease assessment[a] and radiologic scans[dd]	See Table 38 schedule										X		Section 26.4.2
AZD4573 intravenous[ee]	Once weekly (from Cycle 1, Week 1 to end of treatment)[ii]												Section 24.1
Acalabrutinib oral, BID[ff]	Twice daily (from Cycle 1, Week 1 to end of treatment)												Section 24.1
Acalabrutinib drug accountability[gg]	X	X	X	X	X	X	X	X	X				Section 24.5
Disease progression follow-up (SoC)												X	Section 26.1.9.2
Survival Follow-up												X	Section 26.1.9.3

[a] Disease assessments will be done by the Investigator using the Lugano Response Criteria for Non-Hodgkin's Lymphoma (Cheson et al 2014). Additional disease assessments may be performed as clinically indicated.

[b] The SFU visit will be performed 30 days (±7 days) after the last dose of all study drug. Tumour assessments will be repeated at this visit if they have not been performed within 9 weeks if the participant discontinued before or during Week 26, or 12 weeks if the participant discontinued after Week 26.

[c] Vital signs (blood pressure, pulse rate, temperature) will be assessed after the participant has rested for at least 10 mins. Blood pressure and pulse rate will be measured on Day 1 of Cycle 1, Weeks 1-3 at the following timepoints: predose (up to 2 h prior to infusion), 1 h after the start of the infusion (± 10 mins), at end of infusion (up to 10 mins post dose) and then 4 h (± 30 mins) and 6 h (± 30 mins) after start of infusion, from Cycle 1 Week 4, at predose (up to 30 mins prior to infusion), at the end of infusion (up to 30 mins post dose), and at the 30-day SFU. Temperature to be taken pre-infusion (up to 2 h prior to all infusions).

[d] As the study is intended to recruit adults, height should only be measured at Screening. Weight to be measured prior to infusions on Day 1 of each cycle, and at the 30-day SFU visit.

[e] Participants should be in semi-supine position and resting for ≥ 10 mins before the ECGs. Single ECGs for local and central analysis are required at the following timepoints: for Cycle 1, Weeks 1-5 and Cycle 2 Day 1 predose (at the day of infusion prior to infusion) and within 30 mins of the end of infusion; for Cycles 3+ on Day 1 within 30 mins after the end of infusion, and at the 30-day SFU visit.

[f] Cardiac troponin measurements are required at the following timepoints: Cycle 1, Weeks 1-5, predose (within 72 hours prior to infusion) and at 24 h after the start of the infusion, and Cycles 2+ on Day 1 of each cycle, predose (within 72 hours prior to infusion), and at the 30-day SFU visit. Note: either a troponin I or troponin T assay can be used per SoC at the respective hospital. If the hospital has both a SoC troponin I and troponin T assay available, the investigator shall use only one consistently for the duration of the study.

[g] T4, cortisol, ACTH, and TSH to be taken predose (within 72 hours prior to infusion) on Cycle 2, Day 1, and at the 30-day SFU visit.

[h] ECHO should be done within 14 days after an abnormal ECG finding (eg, T-wave inversion/flattening) or as soon as possible when clinically indicated. If an ECHO cannot be taken, a MUGA scan to assess LVEF will be done. In case of any T-wave abnormality, the ECHO (or MUGA) should be repeated at the 30-day follow-up visit to address the question of recovery, during the off-treatment period.

[i] Haematology testing should be measured at Cycles 1, 2, and 3 predose (within 72 h prior to infusion) and 24 h after the start of the infusion. From Cycle 4 onwards, haematology testing should be predose (within 72 h prior to infusion) and (if clinically indicated) 24 h after the start of the infusion. A sample will also be drawn at the 30-day SFU. The Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF.

[j] Coagulation testing should be measured at Cycles 1, 2, and 3 predose (within 72 h prior to infusion) and 24 h post-infusion of AZD4573. For Cycles 4-8, predose (within 72 h of infusion); the 24-h sample can be omitted unless clinically indicated. For Cycles 9+, on Day 1 of each cycle, an AZD4573 pre-infusion sample will be drawn within 72 h prior to infusion. A sample will also be drawn at the 30-day SFU. The Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF.

[k] Clinical chemistry should be measured at Cycles 1, 2, and 3 predose (within 72 h prior to infusion), and 24 h post-infusion of AZD4573. From Cycle 4 onwards, clinical chemistry testing should be measured predose (within 72 h prior to infusion) and (if clinically indicated) 24 h after the start of the infusion. A sample will also be drawn at the 30-day SFU. The investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF. Clinical chemistry tests do not need to be repeated before first dose if the first-dose visit is within 3 days of the most recently available sample.
In addition, GLDH and CPK will be measured before the first dose in Period 2 for all participants. If GLDH cannot be performed locally, LDH will be analysed locally and a serum sample must be collected for central retrospective GLDH analysis, which will be performed as applicable. Refer to the Laboratory Manual for details.
If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, potassium) and troponin must be done to coincide with the ECG testing.

[l] Urine samples will be collected at the following timepoints: Cycles 1-8, predose AZD4573 (within 72 hours prior to infusion) and within approximately 2 hours after the end of infusion, Cycles 9+ on Day 1 of each cycle, predose AZD4573 and within approximately 2 hours after the end of infusion, and at the 30-day SFU.

[m] Pregnancy test to be performed once every 21 days (± 7 days) prior to initiating a new cycle and at the 30-day SFU visit (serum or urine). Additional testing may be performed at Investigator discretion (eg, in the event of suspected contraception failure).

[n] Lipase and amylase should be evaluated at Cycles 1-8 predose AZD4573 (within 72 hours prior to infusion), Cycles 9+, predose AZD4573 (within 72 hours prior to infusion) on Day 1 of each cycle, and at the 30-day SFU visit.

[o] Participants who are anti-HBc positive, or have a known history of HBV infection, should be monitored every 3 months with a quantitative PCR test for HBV DNA. Any participants testing positive for any hepatitis serology must have PCR testing for verification purposes.

[p] CD4, CD8, CD19, CD16/NK and serum immunoglobulins (IgA, IgM, IgG) will be drawn at Day 1 (predose) of Cycles 2, 4, 7, 9, 13, 16, 19 and every 6 months thereafter (predose), and at the 30-day SFU.

[q] Plasma samples for PK analysis will be taken at the following time points: For Cycle 1, of Weeks 1 and 3 : predose (up to 2 h prior to AZD4573) and 1 h (± 15 mins), 2 h (± 15 mins), 4 h (± 30 mins), 7 h (± 1 h), and 24 h (± 1 h) (ie, Day 2 of dosing) after the start of the infusion.

[r] Pharmacodynamic evaluations for AZD4573 blood samples will be collected at Cycle 1, Week 1 at predose (up to 2 h prior to dosing) and 2 h (± 15 mins), 4 h (± 30 mins), 7 h (± 1 hour), and 24 h (± 2 h) (ie, Day 2) after the start of the infusion.

[s] Pharmacodynamic evaluations for acalabrutinib: blood samples (whole blood) are to be taken predose on Cycle 1, Week 1, predose (up to 2 h prior to dosing and prior to acalabrutinib dose), and on Cycle 1, Week 4, (up to 2 h prior to dosing and prior to acalabrutinib dose).

[t] CCI Samples will be taken for all participants at Cycle 1, Week 1: predose (within 2 h prior to dosing) and 4 h (± 30 mins), 7 h (± 1 h), and 24 h (± 1 h) after start of infusion. If the participant has CCI at 24 h after start of infusion, samples will be drawn at 48 h (-2 h/+12 h prior to infusion), 96 h (- 2 h/+12 h prior to infusion), predose-the-following infusion (within 4 h prior to infusion), and at each point chemistry panel testing is being performed. CCI sampling should be performed the same as for Cycle 1, Weeks 1.

[u] Whole blood for exploratory CCI samples will be collected at Cycle 1, Weeks 1, 3, and 5 predose (within 2 h prior to dosing), Cycle 2, Days 1 and 15 predose (within 2 h prior to dosing), Day 1 of Cycles 3, 5, 6 and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[v] Whole Blood for CCI will be collected at Cycle 1, Weeks 1, 3, and 5 predose (within 2 h prior to dosing), Cycle 2, Days 1 and 15, predose (within 2 h prior to dosing), and on Day 1 of Cycles 3, 5, 6, and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[w] Whole blood samples for CCI will be collected at Cycle 1, Weeks 1 and 3 predose (within 2 h prior to dosing) and 24 h (± 2 h), Cycle 2, Days 1 and 15, predose (within 2 h prior to dosing), Day 1 of Cycles 3, 5, and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[x] Whole blood samples for CCI will be collected at Cycle 1, Weeks 1 and 3 predose (up to 2 h prior to dosing), Cycle 2, Days 1 and 15 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[y] Whole blood for CCI exploratory analysis samples will be collected at, Cycle 1, Week 1 predose (within 2 h prior to dosing), Day 1 of Cycles 2, 3, 5, and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[z] Exploratory blood CCI Whole blood samples will be collected at Cycle 1 Week 1 at predose (within 2 h prior to dosing), 2 h (± 15 mins) and 24 h (± 2 h) after the start of the infusion and on Day 1 of Cycles 2, 3, 5, and 7 predose (within 2 h prior to dosing), and at every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion), and at disease progression/end of treatment. If a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

[aa] An optional saliva sample for genomics initiative research will be taken from consenting participants prior to the first dose of IP in Period 1. If for any reason the sample is not taken before dosing it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

[bb] A biopsy will be taken at disease progression for participants who consent. The disease progression sample may be taken at the SFU visit if not collected previously.

[cc] Bone marrow biopsy and aspirate: CCI [redacted]

[dd] See Table 38 for schedule of disease assessments, including mandatory PET assessments. Disease assessments will be done by the Investigator using the Lugano Response Criteria for Non-Hodgkin's Lymphoma (Cheson et al 2014). Additional disease assessments may be performed as clinically indicated.

[ee] AZD4573 is to be administered as an absolute (flat) dose, 2-h (± 15 mins) IV infusion on a once-weekly schedule.

[ff] Acalabrutinib 100 mg oral capsule to be given twice per day.

[gg] Participant-reported drug administration for acalabrutinib needs to be done on every AZD4573 dosing day, ideally prior to dosing (± 24 h) and is also to be done after the last acalabrutinib capsule is taken and the leftover capsules returned to site. Drug accountability for acalabrutinib will occur every 2 weeks, (on an AZD4573 dosing day, ideally prior to dosing [± 24 h]).

[hh] If a participant is attending Cycle 9+ visits according to a modified schedule, in which AZD4573 is not infused and assessments are not performed every week, the Day 1 assessments should be performed at least once per cycle.

[ii] The End of Treatment visit is the last visit attended by the participant prior to the 30-Day SFU on the study. At this visit, the participant does not receive IMP and should undergo the applicable assessments associated with the Cycle and visit they have reached, plus those shown in the "Disease Assessment/End of Treatment" column of the SoA.

[jj] AZD4573 should be administered at least 5 days apart

Abbreviations: ACTH = adrenocorticotropic hormone; BID = twice daily; CMV = cytomegalovirus; CSP = clinical study protocol; ECG = electrocardiogram; eCRF = electronic case report form; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; GLDH = glutamic dehydrogenase; Ig = immunoglobulin; CCI [redacted] LTFU = long-term follow-up; CCI [redacted] MUGA = multigated acquisition; CCI [redacted] PCR = polymerase chain reaction; PK = pharmacokinetics; SFU = safety follow-up; SoC = standard of care; T4 = thyroxine; TLS = tumour lysis syndrome; TSH = thyroid-stimulating hormone.

20 INTRODUCTION – MODULE 2

20.1 Study Rationale – Module 2

Mantle cell lymphoma (MCL) is clinically characterised by its heterogenous behaviour, ranging from indolent disease that may not require therapy for many years, to aggressive disease with poor prognosis. Although MCL generally responds to initial treatment, a majority of patients relapse (Goy and Kahl 2011). Treatment options for r/r MCL include immunochemotherapy, molecular targeted therapy including BTK inhibitors, and immunotherapies, including CAR-T therapy (Silkenstedt et al 2021).

Acalabrutinib, a potent and selective BTK inhibitor, is approved by the Food and Drug Administration (FDA) for the treatment of adults with MCL who have received at least one prior therapy. In a Phase II study of acalabrutinib involving 124 participants with relapsed or refractory (r/r) MCL, 81% of participants had a complete response (complete response [CR], 40%) or partial response (PR 41%) after a median of 15.2 months of follow-up. Kaplan-Meier (KM) estimates of median duration of response (DoR), progression-free survival (PFS) and overall survival (OS) were not reached (Wang et al 2018). At long-term follow-up after a median of 38.1 months, the median DoR was 28.6 months (95% confidence interval (CI) 17.5-39.1 months] and median PFS was 22.0 months (16.6-33.3 months) (Wang et al 2020).

The combination of AZD4573 and acalabrutinib may yield greater clinical benefit than either treatment alone. The effect of acalabrutinib in lowering the apoptotic threshold by induction of pro-apoptotic proteins or reduction of anti-apoptotic proteins (Deng 2017a*)* is expected to play an additive or synergistic role in targeting the apoptotic defects when administered in combination with AZD4573.

20.2 Acalabrutinib Background

For background information on AZD4573, please refer to Section 2.2.

Acalabrutinib is also known as ACP-196 and Calquence®. Calquence is approved in the United States and is either approved or under regulatory assessment in other countries as:

- Monotherapy for the treatment of adult patients with MCL who have received at least one prior therapy.
- Monotherapy and in combination with obinutuzumab for the treatment of adult patients with CLL or small lymphocytic lymphoma (SLL).

Acalabrutinib is a selective, irreversible small molecule BTK inhibitor. In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Acalabrutinib and its major metabolite ACP-5862 inactivate BTK

by forming a covalent bond with a cysteine residue in the kinase active site. This leads to inhibition of signaling through the B-cell receptor (BCR) in sensitive cells. In nonclinical and clinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and survival.

20.2.1 Clinical Experience with Acalabrutinib

As of 30 October 2020, more than 6000 participants have participated in acalabrutinib clinical studies, with approximately 4500 participants receiving acalabrutinib as monotherapy or in combination with other agents in the oncology program. Clinical studies have included participants with haematological malignancies, solid tumours, or rheumatoid arthritis, and participants who are healthy subjects or those with mild to moderate hepatic impairment.

No DLTs have been identified in any studies for acalabrutinib monotherapy and very few with acalabrutinib (given as 100 mg twice daily) in combination with other agents. Important identified risks for acalabrutinib are haemorrhage, atrial fibrillation/flutter, infections, cytopenias, and second primary malignancies. Transaminase elevations (ALT/AST) are considered an important potential risk when the drug is given as monotherapy.

Efficacy data summarised below are based on two pivotal clinical studies in CLL/SLL (ACE-CL-007 and ACE-CL-309) and 3 supportive clinical studies in CLL/SLL (ACE-CL-001, ACE-CL-003, and 15-H-0016). Assessment of overall response was based on modified International Workshop on Chronic Lymphocytic Leukemia (iwCLL) response criteria (Hallek et al 2008) for CLL/SLL participants, with incorporation of the clarification for treatment-related lymphocytosis (Cheson et al 2012).

Ongoing Phase III Pivotal Studies in CLL

Efficacy data for acalabrutinib monotherapy (100 mg twice daily) as well as efficacy data for the combination of acalabrutinib 100 mg twice daily with obinutuzumab from two pivotal ongoing Phase III studies in previously untreated CLL (ACE-CL-007; CCI [redacted], and r/r CLL (ACE-CL-309; CCI [redacted]

Study ACE-CL-309 enrolled and randomised a total of 310 participants CCI [redacted] Acalabrutinib demonstrated a 69% reduction in risk of Independent Review Committee (IRC)-assessed disease progression or death compared with idelalisib + rituximab /bendamustine and rituximab (IR/BR; hazard ratio [HR] = 0.31 [95% CI: 0.20, 0.49], $p < 0.0001$). The clinical benefit with acalabrutinib was further demonstrated by a clinically relevant improvement in DoR for acalabrutinib compared with IR/BR, both by IRC assessment (HR = 0.33) and Investigator-assessment (HR = 0.20), and a significant

prolongation of time to next treatment (TTNT) for acalabrutinib compared with IR/BR (HR = 0.35; p < 0.0001).

Study ACE-CL-007 enrolled and randomised a total of 535 participants [redacted]. Acalabrutinib + obinutuzumab demonstrated a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab + chlorambucil, with a 90% reduction in risk of disease progression or death (HR = 0.10 [95% CI: 0.06, 0.17]; p < 0.0001). Acalabrutinib monotherapy also demonstrated a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab + chlorambucil, with an 80% reduction in risk of disease progression or death (HR = 0.20 [95% CI: 0.13, 0.30]; p < 0.0001). The clinical benefit with acalabrutinib was further demonstrated by a significant prolongation of TTNT compared with obinutuzumab + chlorambucil for both acalabrutinib + obinutuzumab (HR=0.14 [95% CI: 0.08, 0.26]; p < 0.0001) and acalabrutinib monotherapy (HR = 0.24 [95% CI: 0.15, 0.40]; p < 0.0001).

Supportive Studies

Efficacy data for acalabrutinib monotherapy (100 mg twice daily) as well as efficacy data for the combination of acalabrutinib 100 mg twice daily with obinutuzumab from 3 supportive ongoing studies in CLL: ACE-CL-001 [redacted], 15-H-0016 [redacted], and ACE-CL-003 [redacted]

A total of 300 participants received acalabrutinib in the 3 supportive studies, including 166 r/r participants and 134 previously untreated participants. The efficacy results in the supportive studies in participants with r/r and previously untreated CLL are consistent with the results of the pivotal studies. Investigator assessed objective response rate (ORR) in all studies ranged from 87.5% to 100%. Across all cohorts, 6.0% of participants achieved CR, and 85.3% of participants achieved PR as a best response. The median DoR (PR or better) was not reached in any of the cohorts (range: 0.07+ to 51.3+ months).

Acalabrutinib, is approved by the FDA for the treatment of adults with MCL who have received at least one prior therapy. In a Phase II study of acalabrutinib involving 124 participants with r/r MCL, 81% of participants had a CR (40%) or PR (41%) after a median of 15.2 months of follow-up. Kaplan-Meier estimates of median DoR, PFS, and overall survival (OS) were not reached (Wang et al 2018). At long-term follow-up after a median of 38.1 months, the median DoR was 28.6 months (95% CI 17.5-39.1 months] and median PFS was 22.0 months (16.6-33.3 months) (Wang et al 2020).

Acalabrutinib has also been preliminarily assessed as monotherapy in patients with r/r de novo DLBCL (Dreyling et al 2018, Dyer et al 2018). In the latter study, among 21 participants enrolled, an ORR of 24% (19% CRs) was observed.

For more detailed information on the clinical experience for acalabrutinib, refer to the CCI

20.3 Benefit/Risk Assessment – Module 2

For more detailed information about the known and expected benefits and potential risks of AZD4573, please refer to Section 2.3 CCI

More detailed information about the known and expected benefits and potential risks of AZD4573 and acalabrutinib in combination are summarised below. CCI

20.3.1 Risk Assessment

Important identified risks for acalabrutinib are:

- Haemorrhage
- Atrial fibrillation
- Infections
- Cytopenias
- Second primary malignancies

Potential for overlapping toxicities between AZD4573 and acalabrutinib include TLS, haemorrhage, cytopenias, infection including hepatitis B reactivation, gastrointestinal toxicities (nausea, vomiting, and diarrhoea), and liver enzyme abnormalities (Grade 3 and Grade 4 transaminase elevations) with the important potential risk of hepatic injury (Table 25).

Detailed descriptions of safety concerns and management are provided in Section 26.1. Investigators should be particularly alert to the possibility of TLS, significant bleeding and infection, including opportunistic and fungal infections, and care must be taken to monitor platelets and neutrophil counts in accordance with the SoA and more frequently as clinically indicated. ‘Rescue medications’, including platelet transfusions and granulocyte-colony-stimulating factor (G-CSF), are permitted at any time during the study, at the discretion of the Investigator. Specific and detailed guidance is also given in this protocol regarding the management of events of hepatic dysfunction or toxicity.

Several measures, including project-specific, safety-related inclusion/exclusion criteria, physical examinations, evaluation AEs/SAEs, and laboratory testing throughout the study and study treatment modifications and toxicity management guidelines have been incorporated into the study protocol to mitigate any potential or identified risks associated with combining these agents. For further information, refer to the reference safety information for AZD4573 and/or Calquence accordingly.

Table 25 Risk Assessment – AZD4573 Monotherapy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention AZD4573 Monotherapy		
Diarrhoea	Diarrhoea is an identified risk for AZD4573.	Refer to Section 26.1.10.2
Nausea and vomiting	Nausea and/or vomiting are identified risks for AZD4573.	Refer to Section 26.1.10.3
Infections	Infection is an important potential risk for AZD4573.	Refer to Section 26.1.10.7
Cytopenia	Neutropenia is an important identified risk for participants treated with AZD4573.	Refer to Section 26.1.10.8
Liver chemistry test abnormalities	Grade 3 and Grade 4 transaminase elevations with bilirubin increase are an important identified risk for participants treated with AZD4573.	Refer to Section 17.1.10.9
Hepatic injury	Events of hepatotoxicity have been reported in clinical studies with acalabrutinib however, no causal relationship has been established. Subjects with hepatotoxicity should be monitored for resolution, and dose modification or interruption of acalabrutinib may be indicated. In addition, subjects should be managed according to study protocols as well as institutional guidelines with supportive care.	Refer to Section 17.1.10.9
Tumour lysis syndrome (TLS)	TLS is an important identified risk for AZD4573.	Refer to Section 26.1.10.10
Infection/Bone marrow toxicity with peripheral effect/ lymphoid tissue hypocellularity	Infection / bone marrow toxicity with peripheral effect / lymphoid tissue hypocellularity is an important potential risk for AZD4573.	Refer to Section 26.1.10.13
Pancreatic and Cortical Adrenal Injury (as well as Surveillance for	Pancreatic injury and cortical adrenal injury are potential risks for AZD4573 based on preclinical observations.	Refer to Section 26.1.10.14

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Renal, Thymus, and Spleen Toxicity)		
Drug-drug interactions	Specific drug-drug interaction studies have not yet been performed for AZD4573.	Refer to Section 26.1.10.15
Myocardial ischaemia	Myocardial ischaemia and increased heart rate are considered potential risks for AZD4573.	Refer to Section 26.1.10.16
Study Procedures		
Infusion site reactions	As with other drugs administered intravenously, local infusion site reactions (eg, infusion pain, infusion site reaction, skin or vein irritation) may occur.	Refer to Section 26.1.10.17

Risk Assessment – AZD4573 + Acalabrutinib Combination Therapy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention (s) AZD4573 and acalabrutinib		
Headache	Headache is an identified risk for acalabrutinib.	Refer to Section 26.1.10.1
Diarrhoea	Diarrhoea is an identified risk for AZD4573 and acalabrutinib.	Refer to Section 26.1.10.2
Nausea and vomiting	Nausea and/or vomiting are identified risks for AZD4573 and acalabrutinib.	Refer to Section 17.1.10.3
Hepatitis B reactivation	Serious or life-threatening reactivation of viral hepatitis have been reported in patients treated with acalabrutinib.	Refer to Section 26.1.10.4
Progressive multifocal leukoencephalopathy (PML)	Cases of PML have been reported in patients treated with acalabrutinib.	Refer to Section 26.1.10.5
Haemorrhage	Bleeding events, some fatal, including central nervous system, respiratory, and gastrointestinal haemorrhage, have been reported in patients treated with acalabrutinib.	Refer to Section 26.1.10.6
Infections	Serious infections, including fatal events, have been reported in patients treated with acalabrutinib and it is an important identified risk. Infection is an important potential risk for AZD4573.	Refer to Section 26.1.10.7
Cytopenia	Haematological toxicities including neutropenia, anaemia, and thrombocytopenia have occurred in patients treated with acalabrutinib, and neutropenia is	Refer to Section 26.1.10.8

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	an important identified risk for participants treated with AZD4573 or acalabrutinib.	
Liver chemistry test abnormalities	Transaminase elevations are an important potential risk for patients treated with acalabrutinib, and an important identified risk for participants treated with AZD4573.	Refer to Section 26.1.10.9
Hepatic injury	Self-limiting biochemical events fulfilling potential Hy's law criteria are very common with AZD4573 monotherapy, but there have been no cases of fulminant hepatotoxicity to date.	Refer to Section 26.1.10.9
Tumour lysis syndrome (TLS)	TLS is an important identified risk for AZD4573 and an identified risk for acalabrutinib.	Refer to Section 26.1.10.10
Second primary malignancies	Second primary malignancies, including non-skin cancers, have been reported in patients treated with acalabrutinib.	Refer to Section 26.1.10.11
Atrial fibrillation/flutter	Atrial fibrillation/flutter have been reported in patients treated with acalabrutinib. Heart rate increase is a potential risk for AZD4573, and cases of atrial fibrillation have occurred in participants treated with AZD4573.	Refer to Section 26.1.10.12
Infection/Bone marrow toxicity with peripheral effect/ lymphoid tissue hypocellularity	Infection / bone marrow toxicity with peripheral effect / lymphoid tissue hypocellularity is an important potential risk for AZD4573.	Refer to Section 26.1.10.13
Pancreatic and Cortical Adrenal Injury (as well as Surveillance for Renal, Thymus, and Spleen Toxicity)	Pancreatic injury and cortical adrenal injury are potential risks for AZD4573 based on preclinical observations.	Refer to Section 26.1.10.14
Drug-drug interactions	Specific drug-drug interaction studies have not yet been performed for AZD4573. Acalabrutinib may be affected by agents that reduce gastric acidity (antacids or proton-pump inhibitor).	Refer to Section 26.1.10.15
Myocardial ischaemia	Myocardial ischaemia and increased heart rate are considered potential risks for AZD4573.	Refer to Section 26.1.10.16

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Infusion site reactions	As with other drugs administered intravenously, local infusion site reactions (eg, infusion pain, infusion site reaction, skin or vein irritation) may occur.	Refer to Section 26.1.10.17

The Investigator sites participating in this study are all experienced oncology centres and are well equipped for treating patients with relapsed and refractory disease and in the management of haematological toxicities. Furthermore, the protocol has dose reductions and dose interruption criteria to also allow for the management of any potential dose-related toxicity.

20.3.2 Benefit Assessment

Preliminary anti-tumour activity has been observed with AZD4573 as monotherapy in participants with r/r haematological malignancies in the ongoing Phase I, FTIH, dose-escalation study (D8230C00001; see Section 2.2.6). CCI [redacted]

Clinical benefit in patients with MCL has been reported for other CDK inhibitors. In a Phase II study of MCL participants receiving flavopiridol, PR occurred in 11% (95% CI, 2%-28%) of participants and the median duration of response was 3.3 months (range 2.8-13.2) (Kouroukis et al 2003). In a Phase I study among 16 participants with lymphoma receiving dinaciclib, one participant had MCL; this participant had an 8% reduction in tumour mass (Baiocchi et al 2010).

The addition of agents which in combination could provide more continuous anti-tumour activity may reasonably be expected to significantly enhance clinical benefit with manageable changes to risk. Acalabrutinib , a BTK inhibitor like ibrutinib, has been shown to inhibit proliferation and induce apoptosis in B-cell malignancies (Davis et al 2010, Harrington et al 2016). The latter is likely due to the ability of BTK inhibitors to increase certain pro-apoptotic BCL2 family proteins, like Bim, (Deng 2017a, Deng et al 2017b, Sasi et al 2019) pushing the cancer cells closer to their apoptotic threshold, a mechanism known as ‘apoptotic priming’ (NCCN 2021, Ni Chonghaile et al 2011). Capitalising on this apoptotic priming, addition of AZD4573 following a short lead-in of acalabrutinib in the OCI-LY10 DLBCL xenograft model causes an increase in both the magnitude and duration of anti-tumour response, compared to either monotherapy, as demonstrated by more rapid and robust cleavage of caspase-3 and delayed time to tumour regrowth following treatment cessation (Patent WO2019/058348; data on file, AstraZeneca). Acalabrutinib is a highly selective,

potent, covalent inhibitor of BTK with minimal off-target activity leading to a safety profile that may be attractive for combination strategies.

20.3.3 Overall Benefit/Risk Conclusion

Eligible participants will be r/r to prior treatments for their disease, have received one prior line of therapy, and for whom a clinical study is the best option (in the opinion of the Investigator) for next treatment based on response and/or tolerability to prior lines of therapy. Furthermore, participants will have varying levels of disease burden at study entry and almost certainly have acquired mutations as part of their disease course. Therefore, there is no guarantee that any participant will derive clinical benefit during this study.

AstraZeneca believes the anticipated benefits that may be afforded to participants with r/r haematological malignancies currently outweigh the identified and potential risks associated with AZD4573 in combination with acalabrutinib.

As described, the study design aims to minimise risks and build on the preliminary efficacy seen to date in the ongoing FTIH study (D8230C00001), reflecting clinical responses in a r/r participant population. Thus, the benefit/risk assessment for administration of AZD4573 with acalabrutinib is considered acceptable for participants with r/r MCL.

For an assessment of benefit and risks pertaining to the conduct of this study during the COVID-19 pandemic, refer to Appendix A 11.

21 OBJECTIVES AND ENDPOINTS – MODULE 2

Objectives and Endpoints for Part A are outlined in Table 26. An additional primary objective was included for Module 2, regarding AZD4573 monotherapy in MCL.

Table 26 Objectives and Endpoints – Module 2

Objectives	Endpoints
Primary	
Part A	
• Assess the safety and tolerability of the RP2D of AZD4573 in combination with acalabrutinib (100 mg BID) for participants who are administered AZD4573 monotherapy	• Adverse events (including SAEs), dose modifications, treatment discontinuation due to AE, AESIs, laboratory data, vital signs, and ECG changes
• 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
Secondary	
Part A	
• Assess the plasma PK of AZD4573 (when given alone and in combination with acalabrutinib 100 mg) and acalabrutinib (plus its active metabolite ACP-5862)	• Plasma concentrations and derived PK parameters for AZD4573 for the PK analysis set • Plasma concentrations and derived PK parameters for acalabrutinib and its metabolite ACP-5862 for the PK analysis set

Objectives	Endpoints
Exploratory	
Part A	
• 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): – ORR – Proportion of participants with CR – DoR – TTR – PFS • OS
• Assess the PD of AZD4573 (alone and in combination with acalabrutinib) and the PD of acalabrutinib (in combination with AZD4573)	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BID = twice daily; CR = complete response; CCI [redacted] ECG = electrocardiogram; MCL = mantle cell lymphoma; CCI [redacted] PK = pharmacokinetics; CCI [redacted] RP2D = recommended Phase II dose; SAE = serious adverse event; CCI [redacted]

The study design of Part B of this module will be determined from the data emerging from Part A. Specifics for Part B will be defined in a future protocol amendment.

22 STUDY DESIGN – MODULE 2

Module 2 will not open for enrolment until the RP2D for AZD4573 + acalabrutinib has been established in Part A of Module 1.

22.1 Overall Design

Module 2 is a window study comprising 2 cycles (8 weeks) of AZD4573 monotherapy (Period 1) followed by AZD4573 + acalabrutinib combination treatment (Period 2). It will enrol participants with r/r MCL who have failed at least one line of prior therapy, are not eligible for curative treatment options. AZD4573 will be administered in Part A as monotherapy (Period 1) and in combination with acalabrutinib 100 mg twice daily (Period 2). Cycle 1 of each dosing period has a duration of 35 days; subsequent cycles have a duration of 21 days. AZD4573 should be administered at least 5 days apart.

The AZD4573 monotherapy RP2D includes an intra-patient ramp up; participants will receive AZD4573 6 mg at Cycle 1 Week 1, AZD4573 9 mg at Cycle 1 Week 2, and AZD4573 12 mg from Week 3 and thereafter.

The AZD4573 FTIH study (Study D8230C00001) established the AZD4573 monotherapy RP2D in DLBCL (12 mg once weekly), but the dose setting did not include any MCL participants. Hence, in Part A, Period 1 of Module 2 aims to confirm the AZD4573 monotherapy RP2D in MCL participants. If AZD4573 monotherapy is not tolerated in r/r MCL participants, there will be no dose exploration/dose setting conducted in this study. At this time, it is unlikely that AZD4573 monotherapy would be developed at a dose lower than 12 mg in MCL.

Participants will move from AZD4573 monotherapy to combination treatment (AZD4573 + acalabrutinib) based on the Lugano overall response (Cheson et al 2014). See Table 36 for details.

In Period 2, the safety and tolerability of the RP2D of AZD4573 + acalabrutinib established in Module 1 will be assessed in participants with MCL. As participants will have reached an AZD4573 dose of 12 mg 1QW (the maximum dose in combination with acalabrutinib in dose setting Module 1) during Period 1, a further intra-patient ramp up will not be required in Period 2 Cycle 1. Treatment with AZD4573 + acalabrutinib combination therapy may be continued until disease progression, an unacceptable drug-related toxicity occurs, or the participant withdraws or is withdrawn from the study as defined in the protocol.

The SRC will meet after the first 6 participants have completed Part A, Period 1, Cycle 1, and again after the first 6 participants entering Period 2 have completed Cycle 1. The SRC will

continue to monitor safety and tolerability data for all participants in Part A. For further details refer to Section 27.5.

The data cut-off for the primary analysis of Part A will occur approximately 6 months following last-participant first-dose of AZD4573 monotherapy or when 75% of participants have progressed or died in Part A, whichever occurs first. All available data from Period 1 (AZD4573 monotherapy) and Period 2 (AZD4573 plus acalabrutinib) will be analysed.

Additional data cuts may also be performed.

All participants will be followed for survival until death, loss to follow-up, the Sponsor closes the study, or withdrawal of consent, whichever occurs first.

The study design of Part B of Module 2 will be determined from the data emerging from Part A. Specifics of Part B will be defined in a future protocol amendment.

The final analysis will be conducted at the end of the module.

22.2 Scientific Rationale for Study Design

The study design proposed is based on both preclinical and clinical data. Mcl-1 has been shown to be highly expressed in 2 human MCL cell lines and in tumours from 12 of 36 patients with MCL, and expression appeared to correlate with high-grade morphology (Khoury et al 2003). Aberrant expression of *MCL-1* has recently been implicated in lymphomagenesis (Zhou et al 2001), and it is hypothesised that the expression of *MCL-1* could contribute to the pathogenesis of MCL. CCI [redacted]

CCI

CCI

CCI

CCI

CCI

CCI [redacted] Clinical benefit in participants with MCL has also been reported for other CDK inhibitors. Partial response occurred in 11% (95% CI, 2%-28%) of participants with MCL receiving flavopiridol in a Phase II study, the median DoR was 3.3 months (range 2.8-13.2) (Kouroukis et al 2003). Among 16 participants with lymphoma receiving dinaciclib in a Phase I study, one participant had MCL and an 8% reduction in tumour mass was recorded (Baiocchi et al 2010).

Acalabrutinib, is approved by the FDA for the treatment of adults with MCL who have received at least one prior therapy. In a Phase II study of acalabrutinib involving 124 participants with r/r MCL, 81% of participants had a CR (40%) or PR (41%) after a median of 15.2 months of follow-up. Kaplan-Meier estimates of median DoR, PFS, and OS were not reached (Wang et al 2018). At long-term follow-up after a median of 38.1 months, the median DoR was 28.6 months (95% CI 17.5-39.1 months] and median PFS was 22.0 months (16.6-33.3 months) (Wang et al 2020).

The combination of AZD4573 and acalabrutinib may yield greater clinical benefit than either treatment alone. The effect of acalabrutinib in lowering the apoptotic threshold by induction of pro-apoptotic proteins or reduction of anti-apoptotic proteins (Deng 2017a*)* is expected to play an additive or synergistic role in targeting the apoptotic defects when administered in combination with AZD4573. CCI [redacted] As there are limited data available on AZD4573 monotherapy in patients with MCL, Part A of the Module 2 study design includes a window study of 2 cycles of AZD4573 monotherapy in each participant before starting combination treatment with acalabrutinib. This approach will allow AZD4573 monotherapy dose confirmation in participants with MCL before investigating the anti-cancer activity of the AZD4573 and acalabrutinib combination treatment.

For a monotherapy study using AZD4573 in MCL, participants with at least 2 prior lines of treatment including a BTK inhibitor would normally have been enrolled. Notably, the current study implements a window study design where the BTK inhibitor acalabrutinib will be subsequently added, as a combination treatment, to all participants who do not achieve a treatment response after 2 cycles of AZD4573 monotherapy. Hence, MCL participants who are BTK-inhibitor naive and have progressed after one prior line of treatment can be safely enrolled in the current window study, keeping in mind that they will receive appropriate BTK inhibition per protocol.

23 STUDY POPULATION – MODULE 2

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

Participants must meet the inclusion and exclusion criteria of both the core and module protocol. Where there are differences in stringency or cut-off values, the specific module takes precedence. For example, if haematological medication parameters are stricter in the module than in the core, the Investigator should adhere to the module criteria.

23.1 Inclusion Criteria

Each participant should meet all the inclusion criteria (and none of the exclusion criteria) for this study in order to be assigned to a study cohort. Under no circumstances can there be exceptions to this rule.

NOTE: This Module will be enrolling participants with r/r MCL only.

For inclusion in the study, participants must fulfil all of the following criteria:

1 Participants must meet the eligibility criteria described in Section 5.1.

2 Participants with histologically confirmed r/r MCL for whom a clinical study is the best option (in the opinion of the investigator) for next treatment based on response and/or tolerability to prior lines of therapy.

PART A

- Participants with r/r MCL:
  - Diagnosis must be confirmed by biopsy and be immunohistologically characterised.
  - Tumour tissue must also be available for sending to AstraZeneca for pathology testing.

    All participants in Part A must consent to and provide archival tumour specimens, preferably in the form of a formalin-fixed paraffin embedded block (tissue derived from the diagnostic tumour or a metastatic site). If this is not possible, an appropriate number of slides of freshly prepared unstained 5-micron sections from the archival tumour block may be provided as defined in the study Laboratory Manual. Archival tumour specimens must be obtained within 24 months before the first dose of IP. If archival material is unavailable or unsuitable for use, participants must consent to and undergo a fresh tumour biopsy during the screening period. A fresh biopsy is strongly encouraged and preferred, however, a participant will be enrolled based on the prior pathology report.

3 Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (according to the Lugano criteria [Cheson et al 2014]).

4 Participants must have failed at least one prior therapy for the treatment of current disease and not be eligible for treatment with curative intent (e.g. allogenichaematopoietic cell transplantation [HCT]). Eligible participants include both BTKi-naïve and BTKi-exposed.

5 Adequate haematologic function at Screening, as defined in Table 27:

(a) No growth factor support within 14 days prior to the date of the screening laboratory assessment.

(b) No transfusions within 7 days prior to the date of the screening laboratory assessment.

Table 27 Criteria for Adequate Haematological Function

Category	Parameter	Value
Haematologic	Haemoglobin	≥ 8.0 g/dL
	Absolute neutrophil count	≥ 1000 cells/mm^3 (1.0 × 10^9/L)
	Platelet count	≥ 75,000 cells/mm^3 (75 × 10^9/L) without bone marrow involvement
		≥ 50,000 cells/mm^3 (50 × 10^9/L) with bone marrow involvement

– If indicated, transfusions or growth factors can be administered during the screening period, but such cases of deterioration of haematological function must be discussed with the Medical Monitor, to confirm start of study treatment.

6 **Optional** tumour biopsy on study: Participants are also encouraged to consent to and undergo an optional tumour biopsy at disease progression to support correlative biomarker studies.

7 All participants must be willing and able to provide mandatory baseline bone marrow biopsy/aspirate.

23.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1 Participants must comply with the exclusion criteria described in Section 5.2.

2 Current refractory nausea and vomiting, malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach, extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease,

partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.

3 Prior use of standard anti-lymphoma therapy or radiation therapy within 14 days of receiving the first dose of study treatment.

4 Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists.

5 Requires treatment with strong CYP3A inhibitors or inducers (please refer to Appendix F for a list of strong inhibitors and inducers of CYP3A).

6 Requires treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Participants receiving proton-pump inhibitors who switch to H_2-receptor antagonists or antacids are eligible for enrolment to this study (see Section 24.8.4).

7 Serologic status reflecting active hepatitis B or C infection:

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

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

8 Active Cytomegalovirus (CMV) infection (positive CMV immunoglobulin M [IgM] and positive PCR result).

9 Requires or receiving therapeutic anticoagulants, with the exception of short-acting heparins, within 7 days of first dose of study treatment. Novel oral anticoagulants are allowed except for the initial high dose treatment period.

10 Participants on dual antiplatelet and therapeutic anticoagulant therapy (eg, aspirin and therapeutic doses of low molecular weight heparin).

11 History of or ongoing confirmed progressive multifocal leukoencephalopathy (PML).

23.3 Lifestyle Considerations

Please refer to Section 5.3, in addition to Section 23.3.1.

23.3.1 Meals and Dietary Restrictions – Module 2

Acalabrutinib is best taken with water and can be taken with or without food. As acalabrutinib is metabolised by CYP3A, participants should be strongly cautioned against using herbal remedies or dietary supplements (in particular, St John's wort, which is a potent CYP3A inducer).

Otherwise, participants should maintain their regular diet unless modifications are required to manage an AE such as diarrhoea, nausea, or vomiting.

23.4 Screen Failures

Please refer to Section 5.4.

23.5 Justification for Dose

Part A

The ongoing FTIH study (D8230C00001) has demonstrated that administration of AZD4573 is tolerated in participants with r/r haematological malignancies. The study has established a recommended Phase II dose (RP2D) of AZD4573 monotherapy in DLBCL participants involving intra-patient dose ramp up in Cycle 1 from a starting dose on Day 1 (6 mg), with subsequent titration to the intermediate dose on Day 8 (9 mg), and to the target dose of 12 mg on Day 15, with weekly IV administration thereafter at the target dose (data on file, AstraZeneca). This established dose of AZD4573 monotherapy in DLBCL participants will be administered in Part A, Period 1 of Module 2 to participants with r/r MCL.

Acalabrutinib 100 mg BID is the approved dosage for patients with MCL (Calquence United States Prescribing Information). Module 1 of this study evaluates the safety and tolerability of AZD4573 in combination with acalabrutinib 100 mg BID in participants with DLBCL. The target dose of AZD4573 9 mg was tolerated in combination with acalabrutinib, and the target dose level of 12 mg is being explored in participants with DLBCL (data on file, AstraZeneca).

The dose of AZD4573 administered in combination with acalabrutinib during the combination Period 2 of Module 2 to participants with MCL will be established based on emerging data from Module 1 and will be a dose deemed by the SRC to be tolerated in combination with acalabrutinib in participants with DLBCL (ie, the RP2D in DLBCL).

23.6 End of Study Definition

Please refer to Section 4.5 for the definition of the end of the study. The end of Module 2 is defined as the last scheduled visit or contact of the last participant enrolled in this Module. In addition, the study may be terminated, or individual centres closed at the discretion of AstraZeneca (please refer to Appendix A 9). AstraZeneca may also terminate the module prematurely if concerns for safety arise within this study or in any other study with AZD4573 and/or acalabrutinib.

The data cut-off for the primary analysis will occur approximately 6 months following last-participant first-dose or when 75% of participants have progressed or died in Part A, whichever occurs first.

Any patients still receiving study intervention at the completion of the primary analysis will be able to continue to receive the intervention if still considered to be deriving clinical benefit.

Such patients will continue to be monitored for all SAEs up to 30 days after the last dose of the intervention therapy. Participants may be eligible to enrol in either a future rollover study of AZD4573 monotherapy or a future rollover study of the combination of AZD4573 and other anti-cancer agents, respectively.

The results from Module 2 will be reported to Regulatory Authorities within one year of the end of module.

24 STUDY INTERVENTION – MODULE 2

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

24.1 Study Intervention(s) Administered

24.1.1 Investigational Products

AZD4573 will be administered as an absolute (flat) dose, 2-hour (± 15 minutes) IV infusion once weekly, at least 5 days apart, alone and in combination with acalabrutinib 100 mg twice daily continuously.

AZD4573 and acalabrutinib will be supplied by AstraZeneca. CCI [redacted] Detailed information on the drug products and administration guidelines are in the AZD4573 Handling Instructions and acalabrutinib participant leaflet.

Table 28 Investigational Products

Intervention Name	**AZD4573**	**Acalabrutinib**
Type	Drug	Drug
Dose Formulation	Concentrate for solution for infusion	Capsules
Unit Dose Strength(s)	1.5 mg/mL	100 mg
Dose	Part A Period 1: 12 mg* Part A Period 2: dose to be established based on emerging data from Module 1	100 mg BID
Route of Administration	IV infusion	Oral
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP

Intervention Name	AZD4573	Acalabrutinib
Sourcing	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca
Packaging and Labelling	Study Intervention will be provided in vials. Each vial will be labelled as required per country requirement	Study Intervention will be provided in bottles. Each bottle will be labelled as required per country requirement
Current/Former Name(s) or Alias(es)	AZD4573/ AZ13810325	Acalabrutinib/ACP-196 /Calquence

*In Period 1, target dose of 12 mg achieved through intra-patient ramp up from starting dose on Day 1 (6 mg), with subsequent titration to the intermediate dose on Day 8 (9 mg), and to target dose of 12 mg on Day 15.
Abbreviations: BID = twice daily; IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product.

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines and will be translated into the local language. The labels will fulfil Good Manufacturing Practice Annex 13 requirements for labelling.

All IPs should be kept in a secure place under appropriate storage conditions. The IP label on the vial (AZD4573) or bottle (acalabrutinib) specifies the appropriate storage conditions.

Participants enrolled in this study module will receive AZD4573 alone and in combination with 100 mg acalabrutinib. Acalabrutinib is intended to be administered orally every day, twice daily with approximately 240 mL of water and can be administered without regard to food. Doses should be administered 12 hours apart (a window of ± 1 hour is allowed) at approximately the same times each day. The acalabrutinib capsules should be swallowed intact. Participants should not attempt to open capsules or dissolve in water. If vomiting occurs after taking acalabrutinib, the participant should not retake acalabrutinib until the next scheduled dose.

On the day of PK collection, acalabrutinib capsules should be brought to site by the participant and taken within 5 minutes before initiation of AZD4573. The actual date and time of AZD4573 and acalabrutinib dosing will be recorded.

If an acalabrutinib dose is not taken within the allowed window, it can be taken up to 2 hours after the scheduled time with a return to the normal schedule the same or following day. If it has been > 2 hours, the dose should not be taken, and the participant should take the next dose at the next scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit. If a participant needs to take a dose earlier than scheduled, the participant can take the dose up to 2 hours earlier than the scheduled time except on scheduled site visit days. Participants should make every reasonable effort to take the acalabrutinib on

time. Guidance on co-administration of acalabrutinib with agents that affect gastric pH is provided in Section 24.8.

24.2 Starting Dose, Dose-Escalation Scheme, and Stopping Criteria

Module 2, Part A, Period 1 will confirm in MCL the AZD4573 monotherapy RP2D dose, established in DLBCL in the FTIH study (D8230C00001), as the dose setting in the FTIH study did not include MCL participants. The AZD4573 monotherapy RP2D is 12 mg once weekly with an intra-patient ramp over 3 weeks (1st week 6 mg; 2nd week 9 mg; 3rd week and onwards 12 mg).

In Module 2, Part A, Period 2, the dose of AZD4573 administered in combination with acalabrutinib will be established based on emerging data from Module 1 and will be a dose deemed by the SRC to be tolerated in combination with acalabrutinib in participants with DLBCL (ie, the RP2D in DLBCL).

A study-specific SRC in accordance with its charter, will be responsible for providing ongoing safety surveillance of the study, with regularly scheduled reviews of safety, PK, and other relevant data (see Section 18.6). The SRC will be responsible for making recommendations regarding the conduct of the study.

At any timepoint during the study, the occurrence of a fatal AE deemed related to study therapy (after full etiological work-up and in discussion with the SRC) will result in accrual stoppage and a comprehensive review of safety. In addition, potential safety signals arising from Grade ≤ 4 treatment-related AEs will be reviewed in the context of the overall benefit/risk. On review any event deemed to adversely affect overall benefit risk will trigger an ad hoc SRC for comprehensive safety review.

In the case of PHL, if bilirubin remains elevated (compared to baseline) at 96 hours (-2/+12 hours) after the start of the infusion, the participant must be discontinued from the study and biochemistry followed until resolution. The Sponsor must be notified immediately.

24.3 Definition of Evaluable Participant

In Module 2, Part A, an evaluable participant is any participant who received a dose of study drug.

24.4 Duration of Therapy

Participants will move from AZD4573 monotherapy to combination treatment (AZD4573 + acalabrutinib) based on the Lugano overall response (Table 36) (Cheson et al 2014).

Table 29 Part A - Duration of AZD4573 Monotherapy

Disease Assessment	Lugano 2014 Overall Response	Treatment	Next Scheduled Disease Assessment
Period 1, Cycle 2, Week 3[a]	CR	Continue AZD4573 monotherapy (Period 1, Cycle 3)	Period 1, at Cycle 5, Week 3
	PR	Continue AZD4573 monotherapy (Period 1, Cycle 3)	Period 1, at Cycle 5, Week 3
	SD	Continue AZD4573 monotherapy (Period 1, Cycle 3)[b]	Period 1, at Cycle 5, Week 3
	PD	Start combination therapy (Period 2, Cycle 1)	Period 2, after 2 cycles (Section 26.4.2)
Period 1, Cycle 5, Week 3[a]	CR	Continue AZD4573 monotherapy (Period 1, Cycle 6)	Period 1, after 8 cycles (Section 26.4.2)
	PR	Continue AZD4573 monotherapy (Period 1, Cycle 6) [b]	Period 1, after 8 cycles (Section 26.4.2)
	SD	Start combination therapy (Period 2, Cycle 1)	Period 2, after 2 cycles (Section 26.4.2)
	PD	Start combination therapy (Period 2, Cycle 1)	Period 2, after 2 cycles (Section 26.4.2)

[a] Schedule the disease assessment to ensure availability of Lugano overall response (Cheson et al 2014) before Day 1 of the subsequent cycle.
[b] AZD4573 + acalabrutinib combination treatment (Period 2, Cycle 1) can be started at the discretion of the investigator.
Note: AZD4573 + acalabrutinib combination treatment (Part A, Period 2) shall be started, if the participant develops PD at any time during the AZD4573 monotherapy (Part A, Period 1).
Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

24.5 Preparation/Handling/Storage/Accountability of Interventions

Please refer to Section 6.8 for general instructions and instructions specific to AZD4573.

Acalabrutinib drug accountability

Participant reported drug administration for acalabrutinib needs to be done on every AZD4573 dosing day, ideally prior to dosing (± 24 hours) and is also to be done after the last acalabrutinib capsule is taken and the leftover capsules returned to site. Drug accountability for acalabrutinib will occur every two weeks (on an AZD4573 dosing day, ideally prior to dosing [± 24 hours]).

The returned number of acalabrutinib capsules needs to be counted and the participant will be asked whether or not acalabrutinib was taken according to the instructed dosing schedule.

Deviations from the instructed schedule should be discussed with the participant and recorded both in the source documents and the eCRF.

Discrepancies between the expected and returned number of capsules should be discussed with the participant and recorded in the source documents.

24.6 Measures to Minimise Bias: Randomisation and Blinding

This is an open-label, non-randomised study (please refer to Section 6.9).

24.7 Study Intervention Compliance

AZD4573

Participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

Acalabrutinib

Acalabrutinib drug accountability will be conducted as described in Section 24.5 and this will be recorded by the site. If the participant made an error or dropped/lost capsules the site will need to check that the participant will have sufficient capsules for the following week. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of acalabrutinib capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

24.8 Concomitant Therapy

The Investigator must be informed as soon as possible about any concomitant medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant therapy(ies), including over-the-counter medications, herbal remedies, vaccines, and supplements, taken during the study will be recorded.

24.8.1 Permitted Concomitant Therapy

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as “excluded” as listed in Section 24.8.2. Specifically, participants should receive full supportive care during

the study and treatment with antibiotics, anti-emetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

After the start of AZD4573 and acalabrutinib administration, blood and platelet transfusions are allowed as clinically indicated at any time during the study and can be given as per local institutional guidelines.

Supportive care (eg, recombinant growth factor support) and other medications that are considered necessary for the participant's wellbeing, (eg, bisphosphonates), may be given at the discretion of the Investigator and in accordance with local institutional guidelines.

Concomitant use of paracetamol is permitted but is limited to a maximum dose of 4 grams per day.

AstraZeneca recommends administering non-live inactivated vaccines 72 hours prior to administration of the first dose of any IP to avoid biases in the interpretation of safety data due to the potential overlap of vaccine-related AEs with IP AEs.

Permitted concomitant therapy for the management of safety concerns for AZD4573 and acalabrutinib (including TLS) is specified in Section 26.1.10. For guidance on additional prophylaxis for TLS, see Section 26.1.10.10. Administer appropriate hydration and allopurinol or rasburicase per institutional standards before initiating treatment.

24.8.2 Prohibited Concomitant Therapy

Participants must be instructed not to take any medications, including over-the-counter products, herbal remedies, and supplements without first consulting with the Investigator.

The following medications are considered exclusionary during the study. AstraZeneca must be notified if a participant receives any of these during the study:

- Any investigational anti-cancer therapy.
- Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable.
- Participants may use topical or inhaled corticosteroids as therapy for comorbid conditions. Ongoing use of low-dose systemic corticosteroids (≤ 10 mg/day prednisolone or equivalent is permitted (Section 6.11).
- Warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) are prohibited for all participants in the study. Participants who require anticoagulation prophylaxis before

study treatment start or therapeutic anticoagulation for thrombosis while on study will be allowed to receive anticoagulation with a non-vitamin K inhibitor class of anticoagulants. Should participants require either a vitamin K antagonist or combined administration of antiplatelet and therapeutic anticoagulation while on study, acalabrutinib treatment must be discontinued.

For further restrictions on the concomitant use of therapies and possible drug-drug interactions with AZD4573 and acalabrutinib, please refer to Section 6.11 and Section 24.8.4, respectively.

24.8.3 AZD4573 and Concomitant Therapy

For further specific information on AZD4573 and concomitant therapy, please refer to Section 6.11.

24.8.4 Acalabrutinib and Concomitant Treatments

The effect of agents that reduce gastric acidity (antacids or proton-pump inhibitors) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this study indicate that participants should avoid the use of calcium carbonate containing drugs or supplements for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib. Use of omeprazole, esomeprazole, lansoprazole, or any other proton-pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study treatment exposure. However, the decision to treat with proton-pump inhibitors during the study is at the Investigator's discretion, with an understanding of the potential benefit to the participant's gastrointestinal condition and a potential risk of decreased exposure to acalabrutinib. Although the effect of H_2-receptor antagonists (such as famotidine or ranitidine) on acalabrutinib absorption has not been evaluated, if treatment with an H_2-receptor antagonist is required, the H_2-receptor antagonist should be taken approximately 10 hours before or 2 hours after acalabrutinib.

Acalabrutinib is not a strong direct inhibitor or inducer of CYP isoforms; thus, acalabrutinib, at the currently used clinical doses, is unlikely to be a perpetrator of a drug-drug interaction at the level of inhibition or induction of CYP isoforms. The concomitant use of strong inhibitors/inducers of CYP3A should be avoided (please refer to Appendix F). Because acalabrutinib is metabolised by CYP3A, participants should be strongly cautioned against consumption of grapefruit, grapefruit juice, or Seville orange juice (which contain potent CYP3A inhibitors) or using herbal remedies or dietary supplements (in particular, St. John's wort, which is a potent CYP3A inducer). If a participant requires short-term treatment with a strong CYP3A inhibitor (such as anti-infectives for up to 7 days), interrupt acalabrutinib treatment. From Cycle 2 onwards, if a participant requires a moderate CYP3A inhibitor while on study, decrease acalabrutinib dose to 100 mg once daily. Avoid co-administration of strong

CYP3A inducers. If a participant requires treatment with a strong CYP3A inducer, increase the acalabrutinib dose to 200 mg twice daily during concomitant administration with the strong CYP3A inducer and return to recommended dose of 100 mg twice daily after stopping the strong CYP3A inducer.

Concomitant use of paracetamol is permitted but is limited to a maximum dose of 4 grams per day. For participants dosed with AZD4573 and acalabrutinib non-steroidal anti-inflammatory agents such as ibuprofen should also be avoided.

24.9 Dose Modification

Table 30 provides dose reductions options for acalabrutinib.

Table 30 Acalabrutinib Dose Reduction Options

Starting dose	1st dose reduction[a]	2nd dose reduction
100 mg twice daily	100 mg once daily	Discontinue

[a] When reducing to 100 mg acalabrutinib once daily, the morning dose should be retained. If considering dose reduction, please discuss with the Medical Monitor.

Note: Temporary withholding of acalabrutinib for as little as 7 days can cause a transient worsening of disease in MCL and/or of constitutional symptoms. Transient worsening of disease during temporary interruption of acalabrutinib (eg, for drug-related toxicity, surgery, or intercurrent illness) may not indicate disease progression. In such circumstances, and if medically appropriate, following discussion with the Medical Monitor, participants may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be done to document whether tumour control can be maintained or whether actual disease progression has occurred.

If the dose of acalabrutinib is reduced for apparent treatment-related AE/SAE, the dose of acalabrutinib should not be re-escalated unless the participant tolerates the reduced dose for greater than 4 weeks and at the Investigator's discretion and in consultation with the Medical Monitor. Such re-escalation may be particularly warranted if further evaluation reveals that the AE/SAE that led to the dose reduction was not treatment-related. Any changes to the dosing regimen must be recorded on the appropriate eCRF.

Acalabrutinib dose reduction options are described in and dose modification and discontinuation guidelines for haematological and non-haematological toxicities (excluding abnormal liver chemistry results) are shown below in Table 30. Dose modifications for AZD4573 and acalabrutinib for abnormal liver chemistry results are described in Table 31.

In general, if a participant experiences a Grade 1 or Grade 2 haematological or non-haematological toxicity, no dose modification is required. If a participant experiences a Grade 3 or Grade 4 toxicity, not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and/or the dose reduced (see Table 30 for acalabrutinib reduction options and Table 31 for recommended dose modifications for AZD4573 and acalabrutinib) and supportive therapy administered as required. If the toxicity resolves or reverts to CTCAE Grade ≤ 2 within 21 days and the participant was showing clinical benefit, treatment with study treatment(s) may be restarted.

If the toxicity does not resolve to CTCAE Grade ≤ 2 within 21 days, then the participant should be withdrawn from the study and observed until resolution of the toxicity. Maximal drug interruption allowed for related toxicity for both AZD4573 and acalabrutinib is ≤ 21 consecutive days.

Table 31 Recommended Dose Modifications for AZD4573 and Acalabrutinib

Event[a]	Occurrence	Action with AZD4573	Action with Acalabrutinib
Tumour Lysis Syndrome (TLS) – Howard Modification of Cairo-Bishop Criteria			
Changes in uric acid, potassium, phosphorus, creatinine or calcium, or symptoms suggestive of clinically significant TLS, in the Investigator's judgement	Any	For any abnormal changes present before dosing, initiate supportive therapy and hold drug for up to 7 days. If not resolved, reduce by 1 dose level.	Withhold acalabrutinib until resolved, resume dosing at the same dose level upon resolution.
		For events of Grade 1 or 2 TLS, resume at same dose level upon resolution.	For events of Grade 1 or 2 TLS, resume at same dose level upon resolution.
		For **1st occurrence** of Grade 3 TLS resume at the same dose upon resolution to Grade 1.	For **1st occurrence** of Grade 3 TLS resume at the same dose upon resolution.
		For **2nd occurrence** of Grade 3 TLS, after resolution to Grade 1, reduce dose by one dose level when restarting AZD4573 except events that in the opinion of the Investigator, in consultation with the Medical Monitor, are not dose-limiting. For **subsequent occurrences** of Grade 3 TLS, further rechallenge and dose level to be discussed with the Medical Monitor. For events of Grade 4 TLS, discontinue AZD4573.	For **2nd occurrence** of Grade 3 TLS, after resolution to Grade 1, reduce dose by one dose level when restarting or discontinue acalabrutinib except events that in the opinion of the Investigator, in consultation with the Medical Monitor, are not dose-limiting. For **subsequent occurrences** of Grade 3 TLS, further rechallenge and dose level to be discussed with the Medical Monitor. For events of Grade 4 TLS, discontinue acalabrutinib.

Table 31 Recommended Dose Modifications for AZD4573 and Acalabrutinib

Event[a]	Occurrence	Action with AZD4573	Action with Acalabrutinib
Non-haematological Toxicities (Except Liver Dysfunction)			
Grade 3 or 4 non-haematological toxicities	1st occurrence	Withhold dosing with AZD4573 until the toxicity has resolved to Grade 1, but no longer than 21 days[b]. Adequate supportive therapy as per institutional guidelines should be given. AZD4573 therapy may be resumed at the same dose. No dose modification is required.	Withhold acalabrutinib until recovery to Grade ≤ 2. Restart acalabrutinib at the same dose level.
	2nd and subsequent occurrences	Withhold dosing AZD4573 up to 21 days[b]. Adequate supportive therapy as per institutional guidelines should be given. After resolution to Grade 1, reduce dose by one dose level when restarting AZD4573. If no resolution within 21 days discontinue AZD4573[b]. In case of **subsequent occurrences**, dosing may be modified to skip weekly dose(s) (eg, 2 weeks on/1 week off or to 1 week on/1 to 2 weeks off), after discussing with the Medical Monitor.	Withhold acalabrutinib until recovery to Grade ≤ 2. Restart acalabrutinib with 1 level dose reduction or discontinue (see Table 30).

Table 31 Recommended Dose Modifications for AZD4573 and Acalabrutinib

Event[a]	Occurrence	Action with AZD4573	Action with Acalabrutinib
Haematological Toxicities			
Grade 3 or 4 neutropenia without fever or infection, lasting > 7 days despite growth factor support	1st occurrence	Withhold dosing AZD4573 until Grade ≤ 2 or baseline level. Restart at same dose level following resolution.	Withhold acalabrutinib if Grade 4 neutropenia lasting > 7 days until resolution to Grade ≤ 2 or baseline level and then restart at same dose for **1st occurrence**.
	2nd and subsequent occurrence	Withhold dosing AZD4573 until Grade ≤ 2 or baseline level. Restart with one dose level reduction following resolution. In case of **subsequent occurrences**, dosing may be modified to skip weekly dose(s) (eg, 2 weeks on/1 week off or to 1 week on/1 to 2 weeks off), after discussing with the Medical Monitor.	Withhold acalabrutinib if Grade 4 neutropenia lasting > 7 days until resolution to Grade ≤ 2 or baseline level and then restart at a reduced dose or discontinue (see Table 30).
Grade 3 or 4 neutropenia with infection or fever	1st occurrence	Withhold dosing AZD4573. To reduce the infection risks associated with neutropenia, G-CSF may be administered with AZD4573 if clinically indicated/required as per Institutional practice. Consider secondary prophylaxis with G-CSF as per ASCO/ESMO guidelines. Once the toxicity has resolved to ≤ Grade 2 or to baseline level, AZD4573 therapy may be resumed at the same dose.	Withhold acalabrutinib until infection is resolved, antibiotics no longer required and ANC Grade ≤ 2 or baseline level. Following resolution, resume acalabrutinib with 1 level dose reduction or discontinue (see Table 30).

Table 31 Recommended Dose Modifications for AZD4573 and Acalabrutinib

Event[a]	Occurrence	Action with AZD4573	Action with Acalabrutinib
	2nd occurrence	Withhold dosing AZD4573. Consider using G-CSF as clinically indicated/as per Institutional practice. Follow dose reduction guidelines when resuming treatment with AZD4573 after resolution. Reduce dose by one dose level.	Withhold acalabrutinib until infection is resolved, antibiotics no longer required and ANC Grade ≤ 2 or baseline level. Following resolution, resume acalabrutinib with 1 level dose reduction or discontinue (see Table 30).
	3rd occurrence	Discontinue AZD4573.	Discontinue acalabrutinib.
Grade 3 thrombocytopenia without bleeding	Any	Withhold AZD4573 until Grade ≤ 2 or baseline level. Restart AZD4573 at the same dose level. Continued dosing can be considered at the discretion of the investigator after discussion with the medical monitor.	No action.
Grade 4 thrombocytopenia without bleeding requiring blood or platelet transfusion	1st occurrence	Withhold AZD4573 until Grade ≤ 2 or baseline level. Restart AZD4573 at the same dose level.	Withhold acalabrutinib until Grade ≤ 2 or baseline level. Restart acalabrutinib at the same dose level.
	2nd occurrence	Withhold AZD4573 until Grade ≤ 2 or baseline level. Restart AZD4573 with 1 level dose reduction. If not recovered to Grade ≤ 2 or baseline level discontinue.	Withhold acalabrutinib until Grade ≤ 2 or baseline level. Restart acalabrutinib with 1 level dose reduction or discontinue (see Table 30).
	3rd occurrence	Discontinue AZD4573.	Discontinue acalabrutinib.
Grade 3 or 4 thrombocytopenia with bleeding requiring blood or platelet transfusion	1st occurrence	Withhold AZD4573 until Grade ≤ 2 or baseline level. Restart AZD4573 with 1 level dose reduction. If not recovered to Grade ≤ 2 or baseline level discontinue.	Withhold acalabrutinib until Grade ≤ 2 or baseline level. Restart acalabrutinib with 1 level dose reduction or discontinue (see Table 30).

Table 31 Recommended Dose Modifications for AZD4573 and Acalabrutinib

Event[a]	Occurrence	Action with AZD4573	Action with Acalabrutinib
	2nd occurrence	Discontinue AZD4573.	Discontinue acalabrutinib.

[a] Adverse reactions are graded using National Cancer Institute CTCAE version 5.0. All grades refer to CTCAE grading except for TLS, which uses the Howard modification of Cairo-Bishop criteria (Howard et al 2011).

[b] In cases where more than 21 days are needed, a decision to continue, modify, or discontinue study treatment will be made on a case-by-case basis in consultation with the principal Investigator and the Medical Monitor.

Abbreviations: ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; CTCAE = Common Terminology Criteria for Adverse Events; ESMO = European Society for Medical Oncology; G-CSF = granulocyte-colony-stimulating factor; TLS = tumour lysis syndrome.

Dose modifications for AZD4573 and acalabrutinib for abnormal liver chemistry results are described in Table 32.

Table 32 Recommended Dose Modifications for AZD4573 and Acalabrutinib for Abnormal Liver Chemistry Results

Event[a]	Action	
	AZD4573	Acalabrutinib
Isolated[b] Elevations in ALT, AST, or Bilirubin		
Grade 1 Isolated ALT/AST ≤ 3 × ULN or Isolated Bilirubin ≤ 1.5 × ULN	Maintain current dose level. Monitor ALT, AST, ALP, and bilirubin at least 1x per week.	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per week.
Grade 2 Isolated ALT/AST > 3 to ≤ 5 × ULN or Isolated Bilirubin > 1.5- ≤ 3 × ULN	After 7 days if hepatic enzymes resolve to Grade ≤ 1, rechallenge at same dose level.	Withhold or continue acalabrutinib (at Investigator discretion, after discussion with the Medical Monitor). To prevent disease progression, monitor disease parameters closely. Monitor ALT, AST, ALP, and bilirubin at least 1x per week. After 7 days if hepatic enzymes appear to be improving and acalabrutinib was withheld, restart acalabrutinib at current dose level.

Event[a]	Action	
	AZD4573	**Acalabrutinib**
Grade 3 Isolated ALT/AST > 5-20 × ULN	If recovered to Grade ≤ 1 within 7 days, allow rechallenge at same dose level. If not recovered to baseline level within 7 days, discontinue AZD4573.	Withhold or continue acalabrutinib (at Investigator discretion, after discussion with the Medical Monitor). To prevent disease progression, monitor disease parameters closely. Monitor ALT, AST, ALP, and bilirubin at least 1x per week. After 7 days if hepatic enzymes appear to be improving and acalabrutinib was withheld, restart acalabrutinib with 1 level dose reduction or discontinue.
Grade 3 Isolated Bilirubin > 3-10 × ULN	If recovered to baseline level within 96 hours (-2/+12 hours) of the start of the infusion allow rechallenge at same dose level. If not, discontinue AZD4573	
Grade 4[c] Isolated ALT > 20 × ULN or Isolated Bilirubin > 10 × ULN	Discontinue AZD4573.	Discontinue acalabrutinib.
Grade 4 Isolated elevation (≥ 20 × ULN) in AST without concomitant elevation in ALT ≥ 20 × ULN or concomitant elevation in TBL ≥ 2 × ULN that fails to return to baseline level within 7 days from start of dosing	Discontinue AZD4573.	Discontinue acalabrutinib.
Grade 4[c] Isolated AST elevation ≥ 20 × ULN without concomitant elevation in ALT ≥ 20 × ULN or TBL ≥ 2 × ULN	**1st occurrence** If recovered to Grade ≤ 1 or baseline level within 7 days of the start of the infusion allow rechallenge at same dose level	Withhold or continue acalabrutinib (at Investigator discretion, after discussion with the Medical Monitor). To prevent disease progression, monitor disease parameters closely. Monitor ALT, AST, ALP, and bilirubin at least 1x per week. After 7 days if hepatic enzymes appear to be improving and
	2nd occurrence If recovered to Grade ≤ 1 or baseline level within 7 days of the start of the infusion allow rechallenge with 1 dose level reduction	

Event[a]	Action	
	AZD4573	**Acalabrutinib**
	3rd occurrence Discontinue AZD4573	acalabrutinib was withheld, restart acalabrutinib at current dose level at the **1st occurrence** and with 1 level dose reduction at the **2nd occurrence**. Discontinue acalabrutinib at the **3rd occurrence**.
Concurrent elevations in ALT, AST, or bilirubin (Please also refer to Appendix E for actions to be taken in the event of PHL)		
ALT or AST ≥ 3 × ULN with TBL ≥ 2 × ULN (PHL) **AND** INR ≥ 1.5 × ULN (or ≥ 1.5 × baseline if elevated at baseline) of any duration	Discontinue AZD4573.	Discontinue acalabrutinib.
ALT or AST ≥ 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%	Discontinue AZD4573.	Discontinue acalabrutinib.
ALT or AST ≥ 3 × ULN and TBL ≥ 2 × ULN where TBL does not return to baseline level within 96 hours (-2/+12 hours) from start of dose and/or AST or ALT do not return to baseline level within 7 days from start of dose	Discontinue AZD4573.	Discontinue acalabrutinib.
Grade 3 elevation (≥ 5 × ULN) in ALT or AST with TBL elevation above baseline level or ULN, but < 2 × ULN that do not return to baseline level within 7 days	Discontinue AZD4573.	Discontinue acalabrutinib.
ALT and AST ≥ 3 × ULN with concomitant TBL ≥ 2 × ULN, NO increase in INR ≥ 1.5 × ULN (or 1.5 × baseline), and NO fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%	If recovered to Grade ≤ 1 or baseline level within 96 (-2/+12) hours, rechallenge at same dose level[c]	Withhold acalabrutinib until recovered. Once recovered, restart acalabrutinib at same dose.

[a] Adverse reactions are graded using National Cancer Institute CTCAE version 5.0. All grades refer to CTCAE grading except for TLS, which uses the Howard modification of Cairo-Bishop criteria (Howard et al 2011).

[b] Elevations in ALT or AST are considered isolated if bilirubin remains below Grade 1, and elevations in bilirubin are considered isolated if ALT and AST remain below Grade 1.

[c] Participants who are considered for rechallenge in the event of Grade 4 transaminase increases or PHL must discuss possible risk of hepatotoxicity with the treating physician, who will document this discussion and participant agreement for continued treatment in the medical records.

Note: Adequate supportive therapy as per institutional guidelines should be given for all toxicities.
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; INR = international normalised ratio; PHL = Potential Hy's Law; TBL = total bilirubin; ULN = upper limit of normal.

24.9.1 Retreatment Criteria

Retreatment is defined as the first dose of study drug after a significant period of intentional pause in study drug treatment (other than missed doses, eg, study treatment put on hold until resolution of COVID 19)

Retreatment criteria (criteria to be met before participant restarts study drug infusions [and capsules, as applicable]):

All participants:

1 Participant has recovered from all treatment-related non-haematological toxicity to CTCAE Grade ≤ 2.

2 Recovery of neutrophils ≥ 1000/μL and platelets ≥ 50,000/μL.

3 Participant has recovered from all hepatic toxicity events within the timeframes described in Table 32 above. If biochemical changes in transaminase(s) and total bilirubin are consistent with the definition of Hy's Law, the participant may continue to receive study drug only if all abnormalities have resolved within the timeframes specified in Table 32 above, there are no symptoms of liver injury and INR has not increased above 1.5 × ULN (or 1.5 × baseline). In these circumstances the participant must be made aware of the unknown potential for liver damage with continued exposure to AZD4573 prior to retreatment. Documentation of continued consent is required.

4 Recovery of uric acid to < ULN.

5 Recovery of changes in uric acid, potassium, phosphorus, creatinine or calcium, or symptoms suggestive of TLS as defined in Table 31.

6 In case of any new deterioration in laboratory values, not fulfilling eligibility criteria and deeded as clinically significant by the Investigator, the Medical Monitor must be contacted to discuss whether AZD4573 dosing can be continued.

24.10 Intervention After the End of the Study

Treatment with AZD4573 and acalabrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol, or the patient withdraws or is withdrawn from the study for other reasons.

Patients who discontinue AZD4573 may continue to receive acalabrutinib if they are deriving benefit in the opinion of the Investigator. In addition, patients who discontinue acalabrutinib may continue to receive AZD4573 if they are deriving benefit in the opinion of the Investigator.

25 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL – MODULE 2

25.1 Discontinuation of Study Intervention

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Please refer to Section 7.1 for information on discontinuation of study intervention.

25.1.1 Temporary Discontinuation

Refer to Section 24.2 for information on temporary discontinuation and restarting of study intervention.

25.1.2 Rechallenge

Refer to Section 24.9 for information on rechallenge with study intervention.

25.2 Patient Withdrawal from the Study

Please refer to Section 7.2 for information on participant withdrawal from the study.

In addition for Module 2, participants who experience an AE during the dosing ramp up (Period 1 Weeks 1-3) that result in inability to complete the dosing ramp up will permanently discontinue AZD4573 and exit the study.

25.3 Procedures for Handling Participants Incorrectly Initiated on AZD4573 or Combination Therapy

Please refer to Section 7.3 for information on procedures for handling participants incorrectly initiated on AZD4573 or combination therapy.

25.4 Lost to Follow-up

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

Please refer to Section 7.4 for actions to be taken if a participant fails to return to the clinic for a required study visit.

For handling of discontinuation of specific sites or of the study as a whole please refer to Appendix A 9.

26 STUDY ASSESSMENTS AND PROCEDURES – MODULE 2

- Study procedures and their timing are summarised in the SoA (Section 19.2). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- For Part A, Period 1, the amount of blood collected from each participant for the scheduled assessments, is not anticipated to exceed 440 mL in Cycle 1 (cycle duration 5 weeks), 140 mL in Cycle 2 (cycle duration 3 weeks) and 80 mL in each subsequent cycle (cycle duration 3 weeks). If a participant experiences TLS, maximum 30 mL extra blood will be collected per cycle (5 weeks) for safety reasons. CCI [redacted] Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- In Part A, Period 2, the amount of blood collected from each participant for the scheduled assessments, is not anticipated to exceed 350 mL in Cycle 1 (cycle duration 5 weeks), 140 mL in Cycle 2 (cycle duration 3 weeks) and 80 mL in each subsequent cycle (cycle duration 3 weeks). If a participant experiences TLS, maximum 30 mL extra blood will be collected per cycle (5 weeks) for safety reasons. CCI [redacted] Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

26.1 Safety Assessments

26.1.1 Enrolment and Screening

At enrolment, each potential participant will provide informed consent before starting any study-specific procedures (please refer to Appendix A for Regulatory and Ethical

Considerations). Each potential participant approved for screening is assigned a unique participant enrolment number. If a participant withdraws from the study, then the enrolment number cannot be reused.

Demographic data and other characteristics will be recorded and will include date of birth, race and ethnicity, and alcohol use.

A standard medical, medication and surgical history will be obtained with review of the selection criteria with the participant. Concurrent medical signs and symptoms must be documented to establish baseline severities. Previous and concomitant treatments (coded according to the World Health Organization Drug Dictionary [WHODRUG]) will be collected for each participant. A disease history, including the date of initial diagnosis, staging within 30 days of first dose of AZD4573, prognostic indices/disease profiling for MCL (derived from local laboratory results) and list of all prior anti-cancer treatments, and responses and DoR to these treatments, will also be recorded.

Each participant will undergo screening (see Section 19.2) during the 30 days before admission to confirm eligibility (see Sections 23.1 and 23.2).

26.1.2 Physical Examinations

A complete physical examination, including a standard neurological examination should be completed at Screening and will include, at a minimum: the general appearance of the participant, height, weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Investigators should pay special attention to clinical signs related to previous serious illnesses and new or worsening abnormalities may qualify as AEs.

Symptom-directed physical exams are done thereafter for each dosing day as outlined in the SoA, including the SFU visit (Section 19.2) in Period 1 and Period 2.

26.1.3 Vital Signs

Vital signs will be performed at timepoints specified in the SoA (Section 19.2).

Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

Pulse rate and blood pressure

Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not

available.

Blood pressure and pulse measurements should be preceded by at least 10 minutes of rest for the participant in a quiet setting.

Pulse rate and blood pressure measurement timepoints are:

- Screening

Period 1 and Period 2

- Cycle 1 (Weeks 1 to 3):
  - Predose (up to 2 hours prior to infusion)
  - 1 hour after the start of the infusion (± 10 minutes)
  - At the end of the infusion (up to 10 minutes post dose)
  - 4 hours after the start of the infusion (± 30 minutes)
  - 6 hours after the start of the infusion (± 30 minutes)
- From Cycle 1 Week 4 onwards:
  - Predose (up to 30 minutes prior to infusion)
  - At the end of the infusion (up to 30 minutes post dose) on each dosing day
- 30-Day SFU

Body temperature

Body temperature will be measured in degrees Celsius at the following timepoints in Period 1 and Period 2:

- Predose (up to 2 hours prior to all infusions)

Weight

Weight will be measured in kilograms at the following times:

- Screening

Period 1 and Period 2

- Cycle 1 (weeks 1-3) predose
- Cycle 1 Week 4 onwards, Day 1 of each cycle predose

- 30-Day SFU

26.1.4 Electrocardiograms (ECGs)

ECG will be performed at timepoints specified in the SoA (Section 19.2).

Twelve-lead ECGs will be obtained after the participant has been resting semi-supine for at least 10 minutes before the times indicated. All ECGs should be recorded with the participant in the same physical position where possible.

If an abnormal ECG finding at Screening or baseline is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition. If a clinically significant abnormal ECG finding occurs on study, contact the Medical Monitor.

Single ECGs will be collected for local and central analysis at the following timepoints:

- Screening

Period 1 and Period 2

- Cycle 1, Weeks 1 through 5, and Cycle 2, Day 1:
  - Predose (at the day of infusion prior to infusion)
  - End of infusion (within 30 minutes of end of infusion)
- Cycles 3+ Day 1 of each cycle:
  - Within 30 minutes after the end of infusion
- 30-Day SFU

Any abnormal finding in the ECG tracing will be evaluated by the Investigator and will be specifically documented and registered in the eCRF. Throughout the study, clinically relevant new findings or worsening of a pre-existing finding in the ECGs (parameters or abnormal findings in the tracing) must be considered an AE and must be recorded in the AE CRF form.

If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, potassium), and troponin I/troponin T must be done to coincide with the ECG testing. Note: either a troponin I or troponin T assay can be used per SoC at the respective hospital. If the hospital has both a SoC troponin I and troponin T assay available, the investigator shall use only one consistently for the duration of the study.

26.1.5 WHO/ECOG Performance Status

ECOG performance status will be assessed at the following times (see Section 19.2):

- Screening

Period 1 and Period 2

- Cycle 1 through Cycle 8:
  - Predose each dose of AZD4573
- Cycles 9+, Day 1 of each cycle:
  - Predose each dose of AZD4573
- 30-day SFU

Performance status should be measured using the ECOG Performance Status Scale (Table 33). It is recommended, where possible, that a participant's performance status be assessed by the same person throughout the study.

Table 33 ECOG Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
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 all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

26.1.6 B Symptoms

Information on B symptoms (eg, unintentional weight loss, fevers, and night sweats) will be collected at the following times (Section 19.2).

- Screening

Period 1 and Period 2

- Cycle 1 through Cycle 8:
  - Predose AZD4573
- Cycles 9+, Day 1 of each cycle:

  - Predose AZD4573
- 30-day SFU

26.1.7 Clinical Safety Laboratory Assessments

For all participants, results of safety laboratory testing (haematology and clinical chemistry at a minimum) must be available within 72 hours prior to dosing and must be reviewed by the Investigator prior to administration of AZD4573 (all cohorts). If clinically indicated, additional clinical laboratory tests and evaluations may be performed by the Investigator (eg, additional haematology/clinical chemistry panels, TLS parameters, liver enzyme tests); these need to be entered into the eCRF.

This study will use local laboratories.

The following laboratory variables will be measured in Period 1 and Period 2.

Haematology: complete blood count (CBC) with automated and/or manual differential including, but not limited to, white blood cell count, haemoglobin, haematocrit, platelet count, ANC, and absolute lymphocyte count (ALC), and blast cells. Haematology should be evaluated before dosing while participants are receiving treatment.

Haematology samples will be collected at the following timepoints:

- Screening

<u>Period 1 and Period 2</u>

- Cycles 1, 2, and 3
  - Predose AZD4573 (within 72 hours prior to infusion)
  - 24 hours after the start of the infusion
- Cycles 4+
  - Predose AZD4573 (within 72 hours prior to infusion)
  - If clinically indicated, 24-hour after the start of the infusion
- 30-day SFU

The Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF.

Haematology tests do not need to be repeated before first dose if the first-dose visit is within 3 days of the Screening sample.

Clinical Chemistry: albumin, chloride, bicarbonate, calcium total, magnesium, phosphorous, glucose (fasting preferred), CK, ALP, ALT, ammonia (where available at local institution; to be tested every 2 weeks), AST, urea, cholesterol, C-reactive protein, creatinine, Factor V (where available at local institution), GGT, lactate dehydrogenase (LDH), phosphate, potassium, sodium, triglycerides, total bilirubin, direct and indirect bilirubin, total protein, uric acid.

Clinical chemistry samples will be collected at the following timepoints:

- Screening

Period 1 and Period 2

- Cycles 1, 2, and 3
  - Predose AZD4573 (within 72 hours prior to infusion)
  - 24 hours after the start of the infusion
- Cycles 4+
  - Predose AZD4573 (within 72 hours prior to infusion)
  - If clinically indicated, 24-hour after the start of the infusion
- 30-Day SFU

The Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF.

Clinical chemistry and haematology tests do not need to be repeated before first dose if the first-dose visit is within 3 days of the Screening sample.

In addition, GLDH and CPK will be measured at Screening for all participants. If GLDH cannot be performed locally, LDH will be analysed locally and a serum sample must be collected for central retrospective GLDH analysis, which will be performed as applicable. Refer to the Laboratory Manual for details.

Coagulation testing includes aPTT (partial thromboplastin time)/PT (prothrombin time), INR, D-dimer (where available at institution), and fibrinogen.

Samples for coagulation testing will be collected at the following timepoints:

- Screening

Period 1 and Period 2

- Cycles 1, 2, and 3
  - Predose AZD4573 (within 72 hours prior to infusion)
  - 24 hours post-infusion
- Cycles 4 through 8
  - Predose AZD4573 (within 72 hours prior to infusion)
  - If clinically indicated, 24-hour after the start of the infusion
- Cycles 9+, on Day 1 of each cycle
  - Predose AZD4573 (within 72 hours prior to infusion)
- 30-Day SFU

The Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted and these need to be entered into the eCRF.

Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. On dosing days, urinalysis should be performed at the following timepoints:

- Screening

Period 1 and Period 2

- Cycles 1 through Cycle 8
  - Predose AZD4573 (within 72 hours prior to infusion)
  - Within approximately 2 hours after the end of the infusion
- Cycles 9+, on Day 1 of each cycle
  - Predose AZD4573 (within 72 hours prior to infusion)
  - Within approximately 2 hours after the end of the infusion
- 30-Day SFU

Cardiac troponin I or troponin T measurements (note: either a troponin I or troponin T assay can be used per SoC at the respective hospital. If the hospital has both a SoC troponin I and troponin T assay available, the investigator shall use only one consistently for the duration of the study.) are required at the following timepoints:

- Screening

Period 1 and Period 2

- Cycle 1, Weeks 1 through 5
  - Predose AZD4573 (within 72 hours prior to infusion)
  - 24 hours post start of the infusion
- Cycles 2+ Day 1 of each cycle
  - Predose (within 72 hours prior to infusion)
- 30-Day SFU

Electrolyte panel: sodium, chloride, calcium, magnesium, potassium.

If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, potassium), and troponin must be done to coincide with the ECG testing.

Supra-renal glands: T4, cortisol, adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH) should be measured at the following timepoints:

- Screening

Period 1 and Period 2

- Cycle 2, Day 1
  - Predose AZD4573 (within 72 hours prior to infusion)
- 30-Day SFU

Pancreas: Lipase and amylase measurements are required at the following timepoints:

- Screening

Period 1 and Period 2

- Cycles 1 through 8:
  - Predose AZD4573 (within 72 hours prior to infusion)

- Cycles 9+, on Day 1 of each Cycle:
  - Predose AZD4573 (within 72 hours prior to infusion)
- 30-Day SFU

Lipase/amylase tests do not need to be repeated before first dose if the first-dose visit is within 3 days of the Screening sample.

TLS monitoring will include: potassium, calcium, phosphate, uric acid, and creatinine. TLS monitoring will be performed at the following timepoints:

Period 1 and Period 2

- Cycle 1, Weeks 1 through 3
  - Predose AZD4573
  - 6 hours (± 30 minutes) after the start of the infusion
  - 24 hours (± 1 hour) after the start of the infusion (and prior to acalabrutinib dosing in Period 2)

Participants showing signs of clinical or laboratory TLS at 6 hours after the start of the infusion must be admitted for in-patient TLS monitoring for a minimum of 24 hours after the start of the infusion and monitored every 4 to 6 hours during this time (or more frequently if clinically indicated).

For each TLS monitoring timepoint, a TLS Monitoring page in the eCRF is to be filled out.

Liver chemistry tests: **For any participant on study who experiences elevated ALT /AST ≥ 3 × ULN and/or elevated total bilirubin ≥ 2 × ULN**: repeated liver chemistry tests (INR, fibrinogen, D-dimer [where available at institution], ALP, ALT, AST, GLDH, CPK, total bilirubin, direct bilirubin, indirect bilirubin) are required at 48 hours (-2/+12 hours) and 96 hours (-2/+12 hours) after the start of the infusion and until resolution of the event. However, in case the event is not resolved within 96 hours the medical monitor should be contacted. If GLDH cannot be performed locally, LDH will be analysed locally and a serum sample must be collected for central retrospective GLDH analysis. Refer to the Laboratory Manual for details.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets PHL criteria at any point during the study. The Investigator participates, together with the

Sponsor, in review and assessment of these cases. Hy's Law (HL) criteria are met if there is no alternative explanation for the elevations in transaminases and total bilirubin levels.

If an unscheduled ECG is done at any time: troponin and an electrolyte panel* must be done to coincide with the ECG testing.

* can include: sodium, calcium, potassium, chloride, phosphate, magnesium.

If a participant is assessed as meeting PHL criteria, please refer to Appendix E.

Hepatitis serology will be conducted at Screening. Hepatitis serology must include hepatitis B surface antigen (HbsAg), hepatitis B surface antibody (anti-HBs), anti-HBc, and hepatitis C (HCV) antibody. Participants who are anti-HBc positive, or have a known history of hepatitis B virus (HBV) infection, should be monitored every 3 months with a quantitative PCR test for HBV DNA (Section 17.1.10.4). In addition, any participants testing positive for any hepatitis serology must have PCR testing for verification purposes.

Pregnancy: a sample for a pregnancy test will be collected from all female participants of childbearing potential at:

- Screening (serum)
- Cycle 1, Week 1:
  - Predose
- Cycles 2+: once every 21 days (± 7 days) prior to initiating a new cycle
- 30-day SFU

Pregnancy tests after Screening may be serum or urine. Urine β-hCG and quantitative serum β-hCG tests are permitted. If a urine β-hCG test is positive or indeterminate, quantitative serum β-hCG will be performed for confirmation. Additional testing may be performed at Investigator discretion for example in the event of suspected contraception failure.

CMV: All subjects will have CMV testing at Screening including serology testing for CMV immunoglobulin (Ig)G and CMV IgM and CMV DNA PCR testing. Subjects must have a negative result for CMV DNA PCR such that CMV DNA is not detected by PCR at Screening, to be eligible for the study. The Screening CMV serologies will be advisory only, to guide investigators in assessing the risk of new infection or reactivation of CMV while on study.

26.1.8 Other Safety Assessments

Monitoring for TLS per the SoA (Section 19.2) and prophylaxis for TLS are outlined in detail in Section 26.1.10.10.

Blood samples for CCI [redacted] will be collected per the SoA (Section 19.2) and as outlined in Section 26.1.7.

Additional safety assessment requirements include:

- **Echocardiograms (ECHOs):** In addition to Screening, an ECHO should be done within 14 days after an abnormal ECG finding (eg, T-wave inversion/flattening) or as soon as possible when clinically indicated. If an ECHO cannot be taken, a multigated acquisition (MUGA) scan to assess left ventricular ejection fraction (LVEF) will be done. In case of any T-wave abnormality, the ECHO (or MUGA) should be repeated at the 30-day SFU visit to address the question of recovery, during the off-treatment period.
- **CD4, CD8, CD19, CD16/NK** cell count and serum immunoglobulins (IgA, IgM, IgG):
  - Screening
  - Day 1 of Cycles 2, 4, 7, 9, 13, 16, 19
    - Predose
  - Every 6 months thereafter (predose)
  - 30-Day SFU

26.1.9 Follow-up

26.1.9.1 30-day SFU Visit

An SFU visit will be performed 30 (± 7) days from the time that study drug(s) are permanently discontinued (see the SoA [Section 19.2]). Tumour assessments will be repeated at this visit if they have not been performed within 9 weeks if the participant discontinued before Week 53, or 12 weeks if the participant discontinued after Week 53.

26.1.9.2 Long-term Follow-up Visits

Participants who discontinue study drug(s) before documented disease progression will be followed according to standard of care (SoC) until documented disease progression or the start of new anti-cancer therapy. Disease progression or start of new anti-cancer therapy will be captured in the eCRF. During this period, only information on any SAEs considered related to IP or study procedures will be collected. If a participant is unable to attend site for this visit, the long-term follow-up may be performed via phone call. Long-term follow-up visits will cease at disease progression or start of a new anti-cancer therapy, whichever comes first. The long-term follow-up will not apply to participants who withdraw consent or are lost to follow-up.

26.1.9.3 Survival Follow-up

All participants will be followed for survival until death, loss to follow-up, AstraZeneca closes the study, or withdrawal of consent, whichever occurs first. Participants will be followed for survival by telephone calls or clinic visits approximately every 3 months. Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants who received investigational product. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information. During this period, information will be collected in the eCRF on survival status and any new anti-cancer therapies, and on any SAEs considered related to study drug(s) or study procedures.

The follow-up for survival should occur every three months, starting 3 months after end of treatment/discontinuation (ie, 3/6/9/12 months after treatment). In case a shorter/longer interval between two follow-up calls occurs the frequency should return to the multiple of 3 months after treatment (eg, 3/6/9/12 months after treatment and so on).

26.1.10 Prevention and Management of Safety Concerns for AZD4573 in Combination with Acalabrutinib

This section provides recommendations for treatment of potential toxicities associated with acalabrutinib, or the combination of AZD4573 with acalabrutinib, and guidance about modifying the doses of acalabrutinib and AZD4573 due to those toxicities. For complete safety information refer to CCI and Calquence United States Prescribing Information.

Generally, Grade 1 or 2 non-haematological and/or haematological toxicities do not require AZD4573 or acalabrutinib dose reductions and should be managed as medically indicated (with or without short dose interruptions) by the treating physician. Grade 3 and 4 toxicities require dose modifications, temporary treatment interruptions, or discontinuation of AZD4573 and acalabrutinib. These are described in Table 31 and Table 32.

26.1.10.1 Headache

Headache is an identified risk for acalabrutinib. Participants with headache should be managed per institutional guidelines with supportive care and diagnostic evaluations as clinically indicated.

Note: encouraging adequate hydration for participants experiencing headaches has anecdotally been helpful in some cases.

26.1.10.2 Diarrhoea

Diarrhoea is an identified risk for AZD4573 and acalabrutinib. Participants with diarrhoea during therapy should be managed per institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated. After excluding infectious aetiologies, symptomatic management should be considered. Participants experiencing prolonged or severe diarrhoea should be closely monitored and managed as appropriate if dehydration and/or electrolyte abnormalities are observed. Participants should be made aware of the risk of possible overlapping toxicities of diarrhoea while receiving combination study treatments.

Prophylaxis for diarrhoea with atropine is strongly recommended for all participants enrolled into the study as an anti-cholinergic drug, administered at 0.5 mg subcutaneously 15 to 30 minutes prior to all scheduled AZD4573 infusions. In the event of multiple episodes of diarrhoea despite atropine prophylaxis, one additional atropine dose may be considered and administered as outlined above.

In addition, in the event of diarrhoea, participants should remain fully hydrated with additional IV fluids.

26.1.10.3 Nausea and Vomiting

Nausea and/or vomiting are identified risks for AZD4573 and acalabrutinib. Participants with nausea and/or vomiting during therapy should be managed per institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated. Participants experiencing prolonged or severe vomiting should be closely monitored and managed as appropriate if dehydration and/or electrolyte abnormalities are observed. Participants should be made aware of the risk of possible overlapping toxicities of nausea and vomiting while receiving combination study treatments.

Nausea and vomiting are considered important identified risks for AZD4573. Events of nausea and vomiting have been observed in approximately half of all participants dosed with AZD4573 and have occurred at all dose levels tested to date (except 3 mg). Prophylaxis with a 5-HT3 antagonist (eg, ondansetron ± dexamethasone) has been implemented in the Phase I study (D8230C00001) to help alleviate this toxicity.

Regarding the hepatic toxicity events encountered to date with AZD4573, it has been observed that while the biochemical changes of increased transaminase with concomitant elevation in bilirubin seen in some patients could be classified as HL by its strict definition, they do not follow a pattern that is consistent with true HL predictive of hepatic injury, and are therefore 'PHL' cases. The events are rapidly resolved and to date have not led to any clinical sequelae or lasting hepatic injury. Repeated dosing with AZD4573 following these events has demonstrated that there is no consistent pattern of recurrence and no consistent increase in severity of the events if they do recur.

Available transcriptomic and clinical pathology data from the Phase I FTIH study of AZD4573 monotherapy (D8230C00001) suggest the presence of an acute phase response in participants showing signs of liver injury. Thus, anti-inflammatory prophylaxis with steroids (eg, dexamethasone) could be expected to have a beneficial effect on incidence and severity of adverse effects on the liver related to AZD4573.

While, in the absence of a suitably sized control group without prophylactic steroid administration, there is no confirmatory evidence for a positive effect of dexamethasone on liver safety profiles from available Phase I clinical data as yet, assessment of ALT changes from baseline versus cumulative dexamethasone dose suggests a possible trend towards a negative correlation, ie, higher dexamethasone doses being associated with smaller increases in ALT post-baseline.

Therefore, prophylaxis for nausea and vomiting is recommended as follows: administer dexamethasone 8 mg (IV administration preferable but orally also permitted) plus a 5-HT3 antagonist (e.g. ondansetron initially 8 mg to be taken before treatment, then 8 mg every 12 hours for up to 3 days) as anti-emetics for all participants, approximately 30 to 60 minutes prior to all scheduled AZD4573 infusions. Additional doses of dexamethasone 8 mg may be administered if deemed clinically warranted. In addition, in the event of vomiting, participants should remain fully hydrated with additional fluids. Participants experiencing prolonged or severe nausea and vomiting should be closely monitored and managed as appropriate if dehydration and/or electrolyte abnormalities are observed.

26.1.10.4 Hepatitis B Reactivation

Serious or life-threatening reactivation of viral hepatitis have been reported in patients treated with acalabrutinib. Therefore, patients who are anti-HBc positive, or have a known history of HBV infection, should be monitored every 3 months with a quantitative PCR test for HBV DNA. Monitoring should continue until 12 months after last dose of acalabrutinib. Any patient with a rising viral load (above lower limit of detection) should discontinue acalabrutinib and have antiviral therapy instituted and a consultation with a physician with expertise in

managing hepatitis B. Insufficient data exist regarding the safety of resuming acalabrutinib in patients who develop HBV reactivation.

26.1.10.5 Progressive Multifocal Leukoencephalopathy (PML)

Cases of PML have been reported in patients treated with acalabrutinib. Signs and symptoms of PML may include cognitive and behavioural changes, language disturbances, visual disturbances, sensory deficits, weakness, and coordination and gait difficulties.

If PML is suspected, hold further treatment with acalabrutinib until PML is excluded. A diagnostic evaluation may include (but is not limited to):

- Neurologic consultation
- Brain magnetic resonance imaging (MRI)
- PCR analysis for John Cunningham (JC) virus DNA in cerebrospinal fluid

If PML is confirmed, permanently discontinue acalabrutinib.

26.1.10.6 Haemorrhage

Bleeding events, some fatal, including CNS, respiratory, and gastrointestinal haemorrhage, have been reported in patients treated with acalabrutinib. Patients receiving antiplatelet or anticoagulant therapies may be at increased risk of haemorrhage and should be monitored for signs of bleeding. Should patients require either a vitamin K antagonist or combined administration of antiplatelet and therapeutic anticoagulation while on study, acalabrutinib treatment must be discontinued. As a precaution, it is suggested per protocol that acalabrutinib be withheld for at least 3 days pre- and post-surgery. Patients should be made aware of the risk of possible overlapping toxicities of haemorrhage while receiving both study treatments. Patients with haemorrhage should be managed per institutional guidelines or as clinically indicated. Coagulation should be monitored regularly as per the SoA. Avoidance of ibuprofen is advised.

26.1.10.7 Infections

Serious infections, including fatal events, have been reported in patients treated with acalabrutinib. Infection is an important potential risk for AZD4573 and an important identified risk for acalabrutinib. Patients should be made aware of the risk of possible serious infections while receiving combination study treatments. Investigators should be vigilant for signs of infection, especially opportunistic or fungal infections, and the possibility of hepatitis B reactivation. Infections should be managed as per standard clinical practice. In case of Grade 3 infections, the guidelines provided in Table 31 should be followed.

26.1.10.8 Cytopenia

Haematological toxicities including neutropenia, anaemia, and thrombocytopenia have occurred in patients treated with acalabrutinib. Neutropenia is an important identified risk for patients treated with AZD4573 or acalabrutinib. Cytopenia should be considered an overlapping toxicity for AZD4573 and acalabrutinib. In the presence of CTCAE Grade 3/4 neutropenia/leucopoenia/thrombocytopenia/anaemia, patient's blood counts should be monitored, using local laboratories, at least every 48 hours until recovery.

In the clinical setting to date, Grade 3/Grade 4 neutropenia (~ 45% to 50%) has been observed in several patients with an onset around 24 hours after dosing AZD4573 monotherapy. Usually, neutrophils recovered spontaneously even without G-CSF.

Colony-stimulating factors including G-CSF, or pegylated G-CSF have been shown to work rapidly and may be used according to each Investigator site's institutional guidelines. Anti-infective prophylaxis including anti-fungal prophylaxis should be used according to institutional guidelines. Antiviral or cotrimoxazole prophylaxis may not be used unless CD4 helper cell counts are less than 100 to 200 per microlitre.

Primary prophylaxis with G-CSF is not generally recommended. Anti-infective prophylaxis (antibiotics and antifungals) should be given in accordance with local hospital and International National Comprehensive Cancer Network (NCCN)/European Society for Medical Oncology (ESMO)/American Society of Clinical Oncology (ASCO) guidelines.

Please refer to Table 31 for dose modifications due to haematological toxicities.

If the table indicates that the acalabrutinib dose should be reduced and the participant is already on 100 mg/day (see Table 30), acalabrutinib should be discontinued.

26.1.10.9 Liver Chemistry Test Abnormalities and the Risk of Liver Injury

Transaminase elevations are an important potential risk for patients treated with acalabrutinib, and an important identified risk for participants treated with AZD4573. Reactivation of hepatitis B infection has been observed in patients treated with acalabrutinib. Participants should be made aware of the risk of possible overlapping toxicities of transaminase elevations while receiving both drugs. Evidence of abnormal liver chemistry should be monitored as per the protocol guidelines. Increased levels of AST, ALT, or serum bilirubin should trigger an investigation of the cause, which may include viral infection or disease progression with liver infiltration. The Investigator should consider whether the abnormal liver chemistry meets the criteria for expedited reporting.

Bilirubin increase with transaminase increase is included as an important identified risk for AZD4573. Biochemical changes of increased transaminases with concomitant increase in

bilirubin fulfilling criteria for Hy's law have been observed in participants treated with AZD4573. These events resolve rapidly and have to date not been associated with any adverse clinical sequelae or lasting liver damage. Upon rechallenge with AZD4573, there is no consistent pattern of recurrence, nor is there any consistent increase in severity of the events. As such, while the events follow the biochemical definition of Hy's law, the clinical pattern is rapidly self-limiting and does not seem to predict any lasting liver damage.

Participants who experience elevated ALT/AST ≥ 3 × ULN and/or elevated total bilirubin ≥ 2 × ULN after AZD4573 dosing must be closely monitored with repeated liver chemistry tests (INR, fibrinogen, D-dimer [where available at institution], ALP, ALT, AST, GLDH if a GLDH test cannot be performed at the site or locally, LDH will be sufficient), CPK, total bilirubin, direct bilirubin, indirect bilirubin) are required at least every 48 hours (-2/+12 hours) after the start of the infusion and until resolution of the event. CCI will also be collected (see Section 26.8)

If bilirubin fails to resolve within 96 hours (-2/+12 hours) or transaminases fail to resolve within 7 days, or if the event is associated with significant clotting abnormality or clinical symptoms of liver disease, study treatment must be permanently discontinued (the participant remains on study for the 30-day SFU and long-term follow-up [LTFU] visits), and the event must be immediately communicated to AstraZeneca.

For guidance on treating liver toxicity, please refer to Table 32 of this protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets PHL criteria at any point during the study.

Please refer to Appendix E for the process to be followed to identify and appropriately report events of PHL. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

The Investigator will participate, together with the Medical Monitor, in review and assessment of PHL events to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

Regarding the hepatic toxicity events encountered to date with AZD4573, it has been observed that while the biochemical changes of increased transaminase with concomitant elevation in

bilirubin seen in some participants could be classified as HL by its strict definition, they do not follow a pattern that is consistent with true HL predictive of hepatic injury, and are therefore 'PHL' cases. The events are rapidly resolved and to date have not led to any clinical sequelae or lasting hepatic injury. Repeated dosing with AZD4573 following these events has demonstrated that there is no consistent pattern of recurrence and no consistent increase in severity of the events if they do recur.

Available transcriptomic and clinical pathology data from the Phase I, FTIH study of AZD4573 monotherapy (D8230C00001) suggest the presence of an acute phase response in participants showing signs of liver injury. Thus, anti-inflammatory prophylaxis with steroids (eg, dexamethasone) could be expected to have a beneficial effect on incidence and severity of adverse effects on the liver related to AZD4573.

While, in the absence of a suitably-sized control group without prophylactic steroid administration, there is no confirmatory evidence for a positive effect of dexamethasone on liver safety profiles from available Phase I clinical data as yet, assessment of ALT changes from baseline versus cumulative dexamethasone dose suggests a possible trend towards a negative correlation, ie, higher dexamethasone doses being associated with smaller increases in ALT post-baseline.

26.1.10.10 Tumour Lysis Syndrome (TLS)

Tumour lysis syndrome is an important identified risk for AZD4573 and an identified risk for acalabrutinib. **TLS prophylaxis is mandatory for <u>all</u> participants** starting 3 days before the first dose of AZD4573, which should be followed in addition to institutional guidelines.

Tumour lysis syndrome is characterised by the rapid and/or massive release of intracellular constituents (potassium, phosphorus and nucleic acids that can be metabolised to uric acid) following tumour cell lysis, resulting in life-threatening complications including acute kidney injury, arrhythmias, and neurological complications. While TLS can be seen in solid tumours, it is most prevalent in haematological malignancies, particularly bulky, chemosensitive diseases such as AML. Prevention and management of TLS is dependent on risk stratification, and risk-based prophylaxis and management (Howard et al 2011, Howard et al 2016). Participants identified with TLS potential per published risk guidelines (Coiffier et al 2008; Table 33) should be provided with adequate hydration, pharmacological pre-treatment with allopurinol or rasburicase, and be carefully monitored for development of TLS.

Instructions for TLS prophylaxis are presented in Section 26.1.10.10.1, instructions for management of hydration are presented in Section 26.1.10.10.2, and instructions for monitoring and maintenance of TLS are presented in Section 26.1.10.10.3. The Howard

modification of Cairo-Bishop criteria for clinical and laboratory TLS are included in Appendix F.

Laboratory or clinical TLS (please refer to Appendix F for definitions) may trigger dose modification in accordance with guidelines provided in Table 31.

26.1.10.10.1 TLS Prophylaxis

Tumour lysis syndrome prophylaxis is mandatory for **all** patients starting 3 days before the first dose of AZD4573. TLS prophylaxis is mandatory for all infusions as outlined below in Table 34, which provides TLS prophylaxis guidance that should be followed in addition to institutional guidelines. In the event of a discrepancy between the protocol guidelines for the management of TLS and the institutional guidelines of a given Investigator/centre, the Investigator should discuss with the Medical Monitor.

In addition to the criteria outlined in Table 34 below, any participant with creatinine clearance (CrCL) < 80 mL/min must be considered at higher risk of developing TLS and managed appropriately.

TLS prophylaxis/management with rasburicase/allopurinol and IV fluid is permitted at any time during screening and treatment, however rasburicase and allopurinol must not be co-administered (Howard et al 2011; Howard et al 2016; Jones et al 2015)

.

Table 34 Mandatory TLS Prophylaxis Guidance (in Addition to Institutional Guidance)

Type of Cancer	Intermediate/High Risk
NHL	Any LN ≥ 5 cm
	Prophylaxis
Hydration[a]	Oral (1.5-2.0 L/day) plus additional IV fluid: Normal saline 500 mL over 2-4 h prior to AZD4573, then 100-175 mL/h as tolerated to maintain urine output
Antihyperuricemics	Allopurinol 300 mg orally QD beginning 3 days prior to AZD4573 and continuing at least through the end of Week 1[b]. Consider prophylactic rasburicase[c] if baseline uric acid is elevated above ULN[d], LDH > 2 × ULN, or high tumour burden/leukemic cells

[a] Administer more aggressive IV fluid hydration for any participant who cannot tolerate or maintain oral hydration.

[b] Administration of allopurinol should not be stopped at the end of Week 1, however the dose or frequency of administration may be reduced after discussion with the Medical Monitor.

[c] The recommended dose for rasburicase is 0.20 mg/kg IV over 30 minutes. Rasburicase is contraindicated in participants with G6PD deficiency, so participants at higher risk for G6PD deficiency (eg, African or Mediterranean ancestry) should be screened for this condition prior to starting rasburicase. Rasburicase and allopurinol must not be co-administered.

[d] Uric acid levels should be < ULN before each dosing of AZD4573.

Notes: Adequate supportive therapy as per institutional guidelines should be given for all toxicities.
TLS prophylaxis/management with rasburicase/allopurinol and IV fluid is permitted at any time during screening and treatment. Rasburicase and allopurinol must not be co-administered.
Abbreviations: G6PD = glucose-6-phosphate dehydrogenase; IV = intravenous; LDH = serum lactate dehydrogenase; LN = lymph node; NHL = non-Hodgkin lymphoma; QD = once daily; TLS = tumour lysis syndrome; ULN = upper limit of normal.
Modified from Coiffier et al 2008.

26.1.10.10.2 Management of Hydration

Adequate fluid intake for all participants enrolled into the study is mandatory, in particular, around the times of AZD4573 dosing.

All participants are **mandated** to receive IV fluid hydration with normal saline (NaCl 0.9%). For participants at intermediate or high risk for TLS, normal saline 500 mL should be administered over 2 to 4 hours prior to AZD4573 and then continued at a rate of 100 to 175 mL/h as tolerated to maintain urine output.

In case of diarrhoea/nausea/vomiting, more aggressive IV fluid hydration may be needed as clinically indicated. Participants are also encouraged to drink enough fluid before and after each dosing. Please use diuretics carefully, do not use them prophylactically, only if participants have signs of hyper-hydration.

26.1.10.10.3 TLS Prophylaxis, Monitoring, and Management

Please refer to Appendix F for definitions of the Howard modification of Cairo-Bishop criteria for clinical and laboratory TLS.

All participants will receive TLS prophylaxis during the intra-patient ramp up and be monitored for TLS during the first 24 hours post start of dose. Monitoring for TLS includes checking potassium, calcium, phosphate, uric acid, and creatinine. Fluid balance must be monitored according to institutional standards.

Participants 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). If a participant has no signs of laboratory TLS at the 6-hour TLS monitoring assessment, the participant may leave the clinic after the collection of other laboratory samples, as per the SoA, at 7 hours after the start of the infusion and managed as an outparticipant, at the discretion of the Investigator. These participants must return to the clinic the next morning to complete the 24 hour TLS monitoring period as per the SoA (Cycle 1 Weeks 1-3). Participants with TLS at the 6-hour TLS monitoring assessment must be admitted for in-patient TLS monitoring for a minimum of 24 hours after the start of the infusion and monitored every 4 to 6 hours during this time (or more frequently if clinically indicated).

Sites retain the option to hospitalise participants based on clinical judgement, despite normal TLS laboratory results 6 hours after the start of the infusion. Admitting the participant for subsequent dose administrations will be done at Investigator discretion.

Any hospitalisation due to occurrence of an AE must be reported as an SAE, per definition. However, if hospitalisation is purely for the purposes of extended observation then this does not qualify as an SAE and does not need to be reported.

For all participants, results of safety laboratory testing (haematology and clinical chemistry at a minimum) must be available within 72 hours prior to dosing and must be reviewed by the Investigator prior to each administration of AZD4573.

In particular, the uric acid level must be < ULN prior to the start of each AZD4573 infusion.

It is strongly recommended that for all participants with elevated uric acid (hyperuricaemia) and intermediate/high risk of TLS, rasburicase (0.20 mg/kg/d IV over 30 minutes) should be administered as prophylaxis prior to AZD4573 and repeated as clinically indicated thereafter as per local standard.

NOTE: If hyperuricaemia is present at Screening and/or during intra-patient ramp up, SoC therapy for hyperuricaemia should be administered (including IV fluid and rasburicase or allopurinol) to reduce the uric acid levels to < ULN before each administration of AZD4573. Rasburicase and allopurinol must not be co-administered.

Any participant developing laboratory TLS must be treated promptly for electrolyte abnormalities (such as hyperkalaemia) to prevent arrhythmias/seizures and for elevated uric acid (hyperuricaemia) with rasburicase (0.20 mg/kg/d IV over 30 minutes for up to 5 days) to prevent acute renal failure and monitored closely for signs of progression to clinical TLS.

If these measures are inadequate, then haemodialysis represents definitive therapy and should be initiated promptly.

Any participant with hyperkalaemia should receive cardiac monitoring with continuous telemetry for ECG changes associated with potentially life-threatening arrhythmias.

Participants with TLS or suspicion of TLS will remain in hospital to undergo additional investigations until the TLS has resolved.

In participants at high risk of TLS based on high tumour burden/bulky disease (> 10 cm), high proliferation rate (LDH > 2 x ULN), and/or impaired renal function, (Coiffier et al 2008), 24-hour hospitalisation for TLS monitoring is recommended during the intra-patient ramp up.

26.1.10.11 Second Primary Malignancies

Second primary malignancies, including non-skin cancers, have been reported in patients treated with acalabrutinib. The most frequent second primary malignancy was skin cancer (squamous cell carcinoma of the skin). Monitor participants for the appearance of skin cancers. If a participant develops a second primary malignancy (other than non-melanoma skin cancer), discontinue acalabrutinib. Participants with a second primary malignancy should be managed according to institutional guidelines with diagnostic evaluations as clinically indicated.

26.1.10.12 Atrial Fibrillation/Flutter and Sinus Tachycardia

Atrial fibrillation/flutter have been reported in patients treated with acalabrutinib. Atrial fibrillation has also been observed in participants treated with AZD4573, although positive causality has not been established.

CCI

26.1.10.13 Infection/Bone Marrow Toxicity with Peripheral Effect / Lymphoid Tissue Hypocellularity

Infection/bone marrow toxicity with peripheral effect/lymphoid tissue hypocellularity is an important potential risk for AZD4573, based on findings in preclinical studies. Severe infection is considered as an important risk with the combination therapy (Section 26.1.10.7).

As observed in preclinical studies, this important potential risk refers to haematological changes (decreased platelets, red blood cell count/haematocrit, reticulocytes, neutrophils, lymphocytes) that may be/may not be accompanied by secondary infections.

AEs of thrombocytopenia should be managed as deemed appropriate by the Investigator as per standard institutional guidelines and in some cases, management of thrombocytopenia may require platelet transfusions, again these should be done according to local hospital guidelines. If indicated, transfusions or growth factors can be administered during the screening period, but such cases of deterioration of haematological function must be discussed with the Medical Monitor, to confirm start of study treatment.

Common treatable causes of anaemia (eg, iron, vitamin B12, or folate deficiencies and hypothyroidism) should be excluded. In some cases, management of anaemia may require blood transfusions which should be given as per local institutional guidelines.

26.1.10.14 Pancreatic and Cortical Adrenal Injury (as well as Surveillance for Renal, Thymus, and Spleen Toxicity)

Pancreatic injury and cortical adrenal injury are potential risks for AZD4573 based on preclinical observations, however, to date, there are no clinical data suggestive of these risks, but safety surveillance will continue.

Regular complete blood counts, clinical chemistry and coagulation tests will be performed throughout the conduct of the study to monitor for any abnormal laboratory parameters, for example; monitoring of lipase and amylase levels for potential pancreas toxicity, creatinine values and regular urinalysis testing for kidney function, potassium, sodium, cortisol levels along with adrenocorticotropic hormone levels for adrenal glands and TSH for any thyroid toxicity.

26.1.10.15 Drug-Drug interactions

Specific drug-drug interaction studies have not yet been performed for AZD4573. For guidance please refer to Section 24.8.

Acalabrutinib may be affected by agents that reduce gastric acidity (antacids or proton-pump inhibitor). Acalabrutinib is not a strong direct inhibitor or inducer of CYP isoforms and is therefore unlikely to perpetrate drug-drug interactions through affecting CYP isoforms (see Section 24.8).

26.1.10.16 Myocardial Ischaemia and Heart Rate Increased

Myocardial ischaemia and heart rate increased are considered potential risks for AZD4573. There has been an isolated case report of possible myocardial infarction in association with AZD4573, but positive causality could not be established. The same participant experienced heart rate increase during the event of ST-segment elevation myocardial infarction. A thorough evaluation of all participants dosed to date has not revealed any further cases suggestive of myocardial ischaemia or other cardiovascular toxicity causally related to AZD4573 administration.

Safety surveillance related to this potential toxicity will include ECG and troponin I/troponin T measurements for all participants as described in the SoA (Section 19.2). ECG and troponin I/troponin T measurements must be performed for all participants who develop symptoms suggestive of myocardial ischaemia. Note: either a troponin I or troponin T assay can be used per SoC at the respective hospital. If the hospital has both a SoC troponin I and troponin T assay available, the investigator shall use only one consistently for the duration of the study.

26.1.10.17 Management of Other Events: Infusion Site Reactions

As with other drugs administered intravenously, local infusion site reactions (eg, infusion pain, infusion site reaction, skin or vein irritation) may occur and these can be managed according to local institutional guidelines. Implantable port insertions (eg, Portacath) may be considered.

26.2 Adverse Events and Serious Adverse Events

A formal assessment of AEs will occur at the visits marked in the SoA (Section 19.2) , but AEs reported at any time during the study must also be recorded in the eCRF.

Please refer to Section 8.2.

26.2.1 Adverse Events of Special Interest for Acalabrutinib

The following events are adverse events of special interest (AESIs) for acalabrutinib and must be reported to the Sponsor expeditiously in Part A, Period 2, irrespective of regulatory seriousness criteria or causality:

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

Adverse events of special interest for AZD4573 are described in Section 8.2.11.

26.3 Overdose

Please refer to Section 8.3 for general information and information related to AZD4573.

An acalabrutinib overdose is defined as any dose that is higher than the investigated dose. For any participant experiencing an acalabrutinib overdose, observation for any symptomatic side effects should be instituted, and vital signs, biochemical and haematological parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion of acalabrutinib is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

26.4 Efficacy Assessments

All assessments of anti-tumour activity will be done by the investigators using standard response criteria as specified below (Table 36).

26.4.1 Disease Assessment Criteria

Disease staging at baseline for MCL will be done by the modified Ann Arbor classification system (Table 35; Cheson et al 2014). Response assessments will be done by the investigator using standard Lugano 2014 response criteria as specified in Table 36.

Table 35 Lugano Modification of Ann Arbor Staging System (for Primary Nodal Lymphomas)

Stage		Involvement	Extranodal (E) Status
Limited	I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
	II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II Bulky Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors		II as above with "bulky" disease	Not applicable
Advanced	III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
	IV	Additional noncontiguous extralymphatic involvement	Not applicable

Note: Extent of disease is determined by PET-CT for avid lymphomas and CT for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.
Abbreviations: CT computed tomography; PET positron emission tomography.
Reproduced from Table 2.

Table 36 The Lugano Response Criteria for Non-Hodgkin's Lymphoma

Response and Site	PET-CT-Based Response	CT-Based Response
Complete:	**Complete metabolic response:**	**Complete radiologic response (all of the following):**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[b] It is recognised that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial:	**Partial metabolic response:**	**Partial remission (all of the following):**
Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default valve
	At end of treatment, these findings indicate residual disease	When no longer visible 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None

Response and Site	PET-CT-Based Response	CT-Based Response
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease:	**No metabolic response:**	**Stable disease:**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease:	**Progressive metabolic disease:**	**Progressive disease requires at least 1 of the following PPD progression:**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm

Response and Site	PET-CT-Based Response	CT-Based Response
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of pre-existing nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another aetiology (eg, infection, inflammation). If uncertain regarding aetiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

[a] The Lugano 2014 criteria are used in this study for disease assessment. In line with these criteria, it should be clarified that the study definition of CMR is a Deauville score 1-3.

[b] A score of 3 in many participants indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy of myeloid growth factors).

[c] PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Abbreviations: 5PS = 5-point scale; CT = computed tomography; CMR = complete metabolic response; FDG = fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LDi = longest transverse diameter; MRI = magnetic resonance imaging; PET = positron-emission tomography; PPD = product of the perpendicular diameters; SDi = shortest axis perpendicular to LDi; SPD = sum of the product of the diameters. Cheson et al 2014

26.4.2 Disease Assessment Schedule

Baseline tumour assessments will be performed using radiologic imaging by CT with contrast and PET-CT during the screening period. CT scans with contrast will cover neck, chest, abdomen, pelvis and any other disease sites; PET scans will cover the whole body from base of skull to mid-thigh.

Radiologic scans (ie, contrast CT) and PET scans will be performed as specified in Table 37 for Period 1, and Table 38 for Period 2, to confirm PR/CR or as clinically indicated. Unscheduled radiologic scans may be performed at Investigator discretion if deemed clinically indicated.

Table 37 Radiologic Scans and PET Scans for Tumour Assessments During AZD4573 Monotherapy (Period 1)

Timepoints		Required Radiologic Scans[a]	
Screening		Contrast CT	PET
During study[b]	After 8 weeks (~2 cycles)[c]	Contrast CT	
	After 17 weeks (~5 cycles)[c]	Contrast CT	PET
	After 26 weeks (~8 cycles)	Contrast CT	
	After 38 weeks (~12 cycles)	Contrast CT	PET
	After 50 weeks (~16 cycles)	Contrast CT	
	After 62 weeks (~20 cycles)	Contrast CT	PET
	After 74 weeks (~24 cycles)	Contrast CT	
	After 86 weeks (~28 cycles)	Contrast CT	PET
	Every 12 weeks (~4 cycles) thereafter until the end of the study	Contrast CT	
	Every 24 weeks (~8 cycles) thereafter until the end of the study	Contrast CT	PET
30-day Follow-up visit[d]		Contrast CT	PET

[a] Following complete metabolic response, subsequent scheduled PET assessments are no longer mandatory.
[b] Window of ± 1 week for all timepoints.
[c] Mandatory tumour assessments at 8 weeks and 17 weeks must be planned/scheduled to ensure availability of Lugano overall response (Cheson et al 2014) before starting Cycle 3 (Day 1) and Cycle 6 (Day 1), respectively.
[d] Tumour assessments will be repeated at this visit for discontinued participants if not previously performed within the required timeframe ie 9 weeks for participants that discontinued before or during Week 26, and 12 weeks for those that discontinued after Week 26.

Note: At the time the participant moves from Period 1 AZD4573 monotherapy to Period 2 AZD4573 + acalabrutinib combination, contrast CT and PET should be performed.

Table 38 Radiologic Scans and PET Scans for Tumour Assessments During AZD4573 + Acalabrutinib Combination Therapy (Period 2)

Timepoints		Required Radiologic Scans[a]	
During study[b]	After 8 weeks (~2 cycles)[c]	Contrast CT	PET
	After 17 weeks (~5 cycles)[c]	Contrast CT	
	After 26 weeks (~8 cycles)	Contrast CT	PET
	After 38 weeks (~12 cycles)	Contrast CT	
	After 50 weeks (~16 cycles)	Contrast CT	PET
	After 62 weeks (~20 cycles)	Contrast CT	
	After 74 weeks (~24 cycles)	Contrast CT	PET
	After 86 weeks (~28 cycles)	Contrast CT	
	After 98 weeks (~32 cycles)	Contrast CT	PET
	Every 12 weeks (~4 cycles) thereafter until the end of the study	Contrast CT	
	Every 24 weeks (~8 cycles) thereafter until the end of the study	Contrast CT	PET
30-day Follow-up visit[d]		Contrast CT	PET

[a] Following complete metabolic response, subsequent scheduled PET assessments are no longer mandatory.
[b] Window of ± 1 week for all timepoints.
[c] Mandatory tumour assessments at 8 weeks and 17 weeks must be planned/scheduled to ensure availability of Lugano overall response (Cheson et al 2014) before starting Cycle 3 (Day 1) and Cycle 6 (Day 1), respectively.
[d] Tumour assessments will be repeated at this visit for discontinued participants if not previously performed within the required timeframe ie 9 weeks for participants that discontinued before or during Week 26, and 12 weeks for those that discontinued after Week 26.

If a PET-CT is not available, an independent PET and a diagnostic quality CT scan (with contrast) can be used. If PET and CT scans are done on the same day, the PET must be performed prior to the contrast-enhanced CT not to compromise the PET read-out.

Post-screening, the CT portion of a PET-CT (without contrast) may replace a contrast CT per local institutional practice; however, certain radiographic requirements are needed for acceptance, as described in the Site Radiology Manual, provided separately from this protocol.

Where contrast CT is contraindicated or unobtainable, MRI or CT (without contrast) with diagnostic quality (sufficient resolution to allow bi-dimensional measurements) may be used instead. In cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations.

Following complete metabolic response, subsequent scheduled PET assessments are no longer mandatory. For participants with baseline hepatosplenomegaly, the cranial-caudal measurement of the spleen and longest diameter of the liver will be assessed at Screening and all subsequent response evaluations.

All response assessments will be made by the Investigator. All images for the assessment of response will be collected and stored for central review.

Participants should have radiographic tumour measurements done at the participating study centre or an acceptable alternate imaging facility using an identical imaging protocol and similar equipment. The same imaging equipment should be used for all scans whenever possible. The same radiologist should be assigned to read all the scans for a given participant throughout the study.

Participants who discontinue study intervention for reasons other than PD will continue to be scanned for disease response following the same schedule until documented PD, regardless of the start of new anti-lymphoma treatment.

26.4.3 Bone Marrow Assessments

For all participants, bone marrow biopsy and aspirate samples are required for local standard disease profiling (eg, immunohistochemistry, flow cytometry, cytogenetics, fluorescence in situ hybridisation [FISH]). Bone marrow biopsies/aspirates will be collected:

- at Screening (before first dose of AZD4573)
- during the study as part of disease assessment (Cheson et al 2014), when indicated
- as clinically indicated (per SoC)

If bone marrow/aspirate samples are collected on a AZD4573 dosing day, collection should preferably take place pre-infusion. If this is not possible, the collection should take place between 2 hours and 4 hours after the start of the infusion.

If a bone marrow biopsy/aspirate cannot be performed, the Investigator must document in the participant's medical notes the reason why the procedure cannot be performed.

Bone marrow biopsies/aspirates will be read at each site's local laboratory. The results will be entered into the eCRF.

CCI [redacted] Refer to Section 26.10.3 for details.

26.4.4 Tumour Assessment

Initial disease assessments include:

- Staging by Ann Arbor classification (Cheson et al 2014: see Table 35).
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen.
- Complete blood count, platelets, differential, chemistry profile, lactate dehydrogenase
- Whole-body fluorodeoxyglucose (FDG)-positron-emission tomography (PET)/computed tomography (CT) scan.
- Brain imaging (MRI with contrast preferred). MRI of the brain will be performed at Screening only if there is a prior history of CNS involvement or if there are neurologic signs or symptoms present.
- Bone marrow biopsy and aspirate (Section 26.4.1).

DLBCL response criteria: Lugano Response Criteria for Non-Hodgkin's Lymphoma (Cheson et al 2014, see Table 36).

Baseline tumour assessments will be performed using radiologic imaging by CT with contrast and PET-CT covering neck, chest, abdomen, and pelvis within 30 days before the first dose of AZD4573 (Table 37). For participants with baseline hepatosplenomegaly, the cranial-caudal measurement of the spleen and longest diameter of the liver will be assessed at screening and all subsequent response evaluations. Unscheduled radiologic scans may be performed at investigator discretion if deemed clinically indicated. Magnetic resonance imaging may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable. In cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations.

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 (Cheson et al 2014). See Table 36.

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

CT scans

Bi-dimensional measurements will be recorded for lymph nodes ≥ 1.5 cm in longest diameter in the eCRF. Up to a maximum of 6 dominant, measurable lymph nodal lesions should be

assessed as target lesions. These nodes or masses should be selected according to all of the following:

- They should be clearly measurable in at least two perpendicular dimensions.
- If possible, they should be from disparate regions of the body.
- They should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

The perpendicular long and short axis diameters will be measured and recorded in the transverse plane at baseline and follow-up. When appropriate, measurable extranodal disease, defined as extranodal lesions (eg, hepatic nodules) with the longest diameter ≥ 1.0 cm, may be included in the 6 representative, measured lesions.

For the selected target lymph nodal lesions, the sum of the product of the perpendicular diameters will be calculated with the percentage change from baseline for assessment of response and nadir for assessment of progression.

All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, gastrointestinal, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites) and should be factored into overall response assessment.

Visual interpretation of PET-CT scans

The International Working Group criteria for reviewing PET scans were based on visual interpretation, using mediastinal blood pool as the comparator. The current recommendation is to use the 5-point scale (Cheson et al 2014).

Assessment of non-measurable lesions

An overall assessment for all other non-target lesions of present, absent, or present with progression will be recorded and factored into response assessment.

Assessment of new lesions

Appearance of any new lesions more than 1.5 cm in any axis during or at the end of therapy, even if all other lesions are decreasing should be considered progression.

Increased FDG uptake in a previously unaffected site should only be considered progression after confirmation with other modalities (eg, CT, MRI, or X-ray).

In participants with no history of pulmonary lymphoma, new nodules identified by CT are benign and should be considered negative for lymphoma. These lesions typically represent

infectious or inflammatory lesions; therefore, if FDG positive, should not be considered positive for lymphoma in the absence of confirmatory tests, (eg, histology).

The presence or absence of new lesions will be recorded in the eCRF.

26.5 Human Biological Samples

Please refer to Section 8.5 for general information on collection and handling of al samples.

26.6 Pharmacokinetics

Venous blood samples for determination of concentrations of AZD4573 in plasma will be taken at the times presented below.

Samples for PK should be collected from the arm that is not used for the infusion where possible. If this is not possible, then separate lines should be used for drug infusion and sampling. If there is no other option than to use a central line (PICC-line) for drug administration/sample collection, it is mandatory this is a multi-lumen line. This information should be recorded where possible. AZD4573 should be administered using a different lumen from the one which is used for sample collection. The sample collection lumen needs to be flushed twice prior to collecting the sample. AZD4573 administration needs to be paused during the time the samples are collected to prevent sample contamination.

Sample collection date, time, and exact dosing will be recorded for both AZD4573 and acalabrutinib. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

On the day of PK collection, acalabrutinib capsules should be brought to site by the participant and taken within 5 minutes before initiation of AZD4573. The actual date and time of AZD4573 and acalabrutinib dosing will be recorded.

If the participant, in error, takes acalabrutinib at home before coming to the site on the day of PK collection, PK sampling should be conducted at the timepoints listed according to AZD4573 dose provided that the exact time of acalabrutinib dosing was recorded. If there is no record for acalabrutinib dosing, PK should not be collected.

Part A – Period 1

Plasma samples for PK analysis will be taken at the following time points:

- Cycle 1, Weeks 1 through 3 and Cycle 2, Day 1:
  - Predose (within 2 hours prior to AZD4573 administration)
  - 1 hour (± 15 minutes) after the start of infusion

- 2 hours (± 15 minutes) after the start of infusion
- 4 hours (± 30 minutes) after the start of infusion
- 7 hours (± 1 hour) after the start of infusion, and
- 24 hours (± 1 hour) after the start of the infusion.

The timing and frequency of the PK samples may be adjusted during the study, dependent on emerging data, to ensure appropriate characterisation of the plasma concentration-time profiles.

Part A – Period 2

Plasma samples for PK analysis will be taken at the following time points:

- Cycle 1, Weeks 1 and 3:
  - Predose (within 2 hours prior to AZD4573 [and acalabrutinib during Period 2] administration)
  - 1 hour (± 15 minutes) after the start of infusion
  - 2 hours (± 15 minutes) after the start of infusion
  - 4 hours (± 30 minutes) after the start of infusion
  - 7 hours (± 1 hour) after the start of infusion, and
  - 24 hours (± 1 hour) after the start of the infusion (and prior to acalabrutinib dosing in Period 2).

The timing and frequency of the PK samples may be adjusted during the study, dependent on emerging data, to ensure appropriate characterisation of the plasma concentration-time profiles.

26.6.1 Determination of Drug Concentration

Samples for determination of AZD4573, acalabrutinib, and its metabolite ACP-5862 concentrations in plasma will be analysed by Covance Laboratories on behalf of AstraZeneca, using appropriate validated bioanalytical methods. Full details of the analytical methods used will be described in a separate bioanalytical report.

All samples still within the known stability of the analytes of interest (ie, AZD4573) at the time of receipt by the bioanalytical laboratory will be analysed. Incurred sample reproducibility analysis or additional assay development work, if any, will be performed

alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate bioanalytical report.

26.7 Pharmacodynamics

26.7.1 Collection of Samples

Whole blood samples will be collected and immediately processed within 30 minutes on site for CCI [redacted]

In addition, whole blood will be collected at limited timepoints to analyse pharmacodynamic readouts for acalabrutinib.

Mandatory pharmacodynamics (whole blood) samples will be collected at the following timepoints:

Pharmacodynamic Samples for AZD4573 (Site-Isolated PBMCs)

Period 1

- Cycle 1, Weeks 1 and 2
  - Predose (up to 2 hours prior to dosing)
  - 2 hours (± 15 minutes) after the start of the infusion
  - 4 hours (± 30 minutes) after the start of the infusion
  - 24 hours (± 2 hours) after the start of the infusion
- Cycle 1, Week 3
  - Predose (up to 2 hours prior to dosing)
  - 2 hours (± 15 minutes) after the start of the infusion
  - 4 hours (± 30 minutes) after the start of the infusion
  - 7 hours (± 1 hour) after the start of the infusion
  - 24 hours (± 2 hours) after the start of the infusion

Period 2

- Cycle 1, Week 1
  - Predose (up to 2 hours prior to dosing)

- 2 hours (± 15 minutes) after the start of the infusion
- 4 hours (± 30 minutes) after the start of the infusion
- 7 hours (± 1 hour) after the start of the infusion
- 24 hours (± 2 hours) after the start of the infusion (and prior to acalabrutinib dosing in Period 2)

Pharmacodynamic Samples for Acalabrutinib (Whole blood)

Period 2

- Cycle 1, Week 1
  - Predose (up to 2 hours prior to dosing and prior to acalabrutinib dose)
- Cycle 1, Week 4
  - Predose (up to 2 hours prior to dosing and prior to acalabrutinib dose)

CCI must be collected at each sample at each pharmacodynamic timepoint once participants have reached the target dose. Refer to instructions in the Laboratory Manual.

Note: The timing of these samples may be adjusted dependent upon ongoing PK and pharmacodynamic analysis and interpretation.

For storage, re-use and destruction of pharmacodynamic samples, please refer to Appendix C.

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

26.8 Exploratory CCI Samples

CCI samples will be collected from all participants to assess exploratory CCI These samples will be collected as per the timepoints in Section 19.2.

Table 39 CCI Sampling Schedule (All Participants)

Day	Timing for Blood Samples	Window
Screening	At any Screening visit	Not applicable
Period 1: Cycle 1, Weeks 1-3 Period 2: Cycle 1, Week 1	Predose	Within 2 hours before the start of the infusion
	4 hours after the start of the infusion	± 30 minutes
	7 hours after the start of the infusion	± 1 hour

	24 hours after the start of the infusion	± 1 hour
CCI [redacted]	48 hours after the start of the infusion	-2 / +12 hours
	96 hours after the start of the infusion	-2/+12 hours
	Predose the following infusion	Within 4 hours before the start of the infusion
	Each timepoint where chemistry panel testing is performed	Not applicable
Period 1: Any visit from Cycle 1, Week 4 onwards and Period 2: Cycle 1 Week 2 CCI [redacted]	Same schedule as Cycle 1, Weeks 1-3	Not applicable

For all participants, CCI [redacted] samples will be collected during Period 1, Cycle 1, Weeks 1 to 3 and Period 2, Cycle 1, Week 1. In addition CCI [redacted] samples should also be taken at 48 and 96 hours after the start of the infusion (-2 / +12 hours), predose the following infusion (within 4 hours) and whenever chemistry panel testing is being performed, until resolution of the event.

CCI [redacted] sampling should be performed using the timepoints at least at 48 hours and 96 hours after the start of the infusion (-2/+12 hours) as outlined in Table 39 (excluding Screening sample).

26.9 Exploratory Whole Blood Analyses Samples

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

Samples for CCI [redacted] are required and will be collected from all participants.

Mandatory whole blood samples will be collected from all participants as per the schedule in Table 40 (Period 1) and Table 41 (Period 2) and the sections below.

Table 40 Exploratory Whole Blood Analyses Samples (All Participants) - MODULE 2 Period 1

	Timepoints[a]																		
		C1 Week 1			C1 Week 2			C1 Week 3			C1 W5	C2 D1	C2 D15	C3 D1	C5 D1	C6 D1	C7 D1	Tumour Assessment Scans[b]	EOT[c]
Samples	Screening	Pre	Post (2h)	24h	Pre	Post (2h)	24h	Pre	Post (2h)	24h	Pre	Pre	Pre	Pre	Pre	Pre	Pre		
CCI [d]	X	X						X			X	X	X	X	X	X	X	X	X
CCI [e]	X	X						X			X	X	X	X	X	X	X	X	X
CCI [f]	X	X						X				X	X	X	X		X	X	X
CCI	X	X						X				X	X					X	X
CCI [g]	X	X										X		X	X		X	X	X
CCI [h]	X	X	X	X	X	X	X	X	X	X		X		X	X		X	X	X

[a] Timepoints include the following windows: pre-dose = within 2 h prior to dosing; post-dose = 2 h (± 15 min) after start of infusion, and 24h = 24 h (± 2 h) after start of infusion.

[b] Every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion)

[c] Disease progression/End of Treatment; if not collected at End of Treatment, the sample should be collected at the 30d Safety Follow-Up visit

[d] CCI

[e] CCI

[f] CCI

[g] CCI

[h] CCI

Note: For all analytes, if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

Abbreviations: C1W5 = Cycle 1 Week 5; C2D1 = Cycle 2, Day 1; EOT = end of treatment; CCI post = post-dose; pre = pre-dose; 24h = 24 h after infusion; SFU = safety follow-up.

Table 41 Exploratory Whole Blood Analyses Samples (All Participants) - MODULE 2 Period 2

	Timepoints[a]																	
	C1 Week 1			C1 Week 2			C1 Week 3			C1 W5	C2 D1	C2 D15	C3 D1	C5 D1	C6 D1	C7 D1	Tumour Assessment Scans[b]	EOT[c]
Samples	Pre	Post (2h)	24h	Pre	Post (2h)	24h	Pre	Post (2h)	24h	Pre	Pre	Pre	Pre	Pre	Pre	Pre		
CCI [d]	X						X			X	X	X	X	X	X	X	X	X
CCI [e]	X						X			X	X	X	X	X	X	X	X	X
CCI [f]	X		X				X		X		X	X	X	X		X	X	X
CCI	X						X				X	X					X	X
CCI [g]	X										X		X	X		X	X	X
CCI [h]	X	X	X								X		X	X		X	X	X

[a] Timepoints include the following windows: pre-dose = within 2 h prior to dosing; post-dose = 2 h (± 15 min) after start of infusion, and 24h = 24 h (± 2 h) after start of infusion.

[b] Every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion)

[c] Disease progression/End of Treatment; if not collected at End of Treatment, the sample should be collected at the 30d Safety Follow-Up visit

[d] CCI

[e] CCI

[f] CCI

[g] CCI

[h] Exploratory Blood CCI Samples: samples CCI exploratory analysis (for the 24h sample: prior to next acalabrutinib dose)

Note: For all analytes, if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

Abbreviations: C1W5 = Cycle 1 Week 5; C2D1 = Cycle 2, Day 1; EOT = end of treatment; CCI post = post-dose; pre = pre-dose; 24h = 24 h after infusion; SFU = safety follow-up.

26.9.1 Whole Blood for Exploratory [redacted]

Mandatory whole blood samples to enable exploratory [redacted] analysis will be collected as specified below. Note: Collection time begins with the start of the infusion.

- Screening

Period 1 and Period 2

- Cycle 1, Weeks 1, 3, and 5:
  - Predose (within 2 hours prior to dosing)
- Cycle 2, Days 1 and 15:
  - Predose (within 2 hours prior to dosing)
- Day 1 of Cycles 3, 5, 6, and 7:
  - Predose (within 2 hours prior to dosing)
- Every scheduled and unscheduled tumour assessment scan (if on day of infusion, collect pre-infusion)
- Disease progression/End of treatment - if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

26.9.2 Whole Blood for [redacted] Analysis

Mandatory whole blood samples to isolate [redacted] analysis will be collected [redacted] Note: Collection time begins with the start of the infusion.

- Screening

Period 1 and Period 2

- Cycle 1, Weeks 1, 3, and 5:
  - Predose (within 2 hours prior to dosing)
- Cycle 2, Days 1 and 15:
  - Predose (within 2 hours prior to dosing)
- Day 1 of Cycles 3, 5, 6, and 7:
  - Predose (within 2 hours prior to dosing)

- Every scheduled and unscheduled tumour assessment scan (if on day of infusion, collect pre-infusion)
- Disease progression/End of treatment - if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

26.9.3 Whole Blood Samples for [redacted]

Mandatory whole blood samples will be collected from all participants at the timepoints indicated below. [redacted] Note: Collection time begins with the start of the infusion.

- Screening

Period 1

- Cycle 1, Week 1:
  - Predose (within 2 hours prior to dosing)
- Cycle 1, Week 3:
  - Predose (within 2 hours prior to dosing)
- Cycle 2, Days 1 and 15:
  - Predose (up to 2 hours prior to dosing)
- Day 1 of Cycles 3, 5, and 7:
  - Predose (within 2 hours prior to dosing)
- Every scheduled or unscheduled tumour assessment scan (if on day of infusion, collect pre-infusion)
- Disease progression/End of treatment - if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

Period 2

- Cycle 1, Week 1:
  - Predose (within 2 hours prior to dosing)
  - 24 hours (± 2 hours) after the start of the infusion (and prior to acalabrutinib dosing in Period 2)
- Cycle 1, Week 3:
  - Predose (within 2 hours prior to dosing)
  - 24 hours (± 2 hours) after the start of the infusion (and prior to acalabrutinib dosing in Period 2)

- Cycle 2, Days 1 and 15:
  - Predose (within 2 hours prior to dosing)
- Day 1 of Cycles 3, 5, and 7:
  - Predose (within 2 hours prior to dosing)
- Every scheduled or unscheduled tumour assessment scan (if on day of infusion, collect pre-infusion)
- Disease progression/End of treatment - if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

26.9.4 Whole Blood Samples for [redacted]

Mandatory whole blood samples will be collected from all participants at the timepoints indicated below. [redacted] Note: Collection time begins with the start of the infusion.

- Screening

Period 1 and Period 2

- Cycle 1, Week 1:
  - Predose (within 2 hours prior to dosing)
- Cycle 1, Week 3:
  - Predose (within 2 hours prior to dosing)
- Cycle 2, Days 1 and 15:
  - Predose (within 2 hours prior to dosing)
- Every scheduled or unscheduled tumour assessment scan (if on day of infusion, collect pre-infusion)
- Disease progression/End of treatment - if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

26.9.5 Whole Blood for [redacted] Exploratory Analysis

Mandatory whole blood samples will be collected from all participants [redacted] at the timepoints indicated below [redacted] Note: Collection time begins with the start of the infusion.

- Screening

Period 1 and Period 2

- Cycle 1, Week 1:
  - Predose (within 2 hours prior to dosing)
- Day 1 of Cycles 2, 3, 5, and 7:
  - Predose (within 2 hours prior to dosing)
- Every scheduled or unscheduled tumour assessment scan (if on day of infusion, collect pre-infusion)
- Disease progression/End of treatment - if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

26.9.6 Exploratory Blood [redacted] Samples

Mandatory whole blood samples will be collected [redacted] from all participants at the timepoints indicated below. [redacted] Note: Collection time begins with the start of the infusion.

- Screening

Period 1

- Cycle 1, Week 1, Week 2 and Week 3 (AZD4573 first and second ramp-up and target dose):
  - Predose (within 2 hours prior to dosing)
  - 2 hours (± 15 minutes) after the start of the infusion
  - 24 hours (± 2 hours) after the start of the infusion
- Day 1 of Cycles 2, 3, 5, and 7:
  - Predose (within 2 hours prior to dosing)

Period 2

- Cycle 1, Week 1:
  - Predose (within 2 hours prior to dosing)
  - 2 hours (± 15 minutes) after the start of the infusion
  - 24 hours (± 2 hours) after the start of the infusion (and prior to acalabrutinib dosing in Period 2)

- Day 1 of Cycles 2, 3, 5, and 7:
  - Predose (within 2 hours prior to dosing)

- Every scheduled or unscheduled tumour assessment scan (if on the day of infusion, collect pre-infusion)
- Disease progression/End of treatment - if a sample is not taken at End of Treatment, a sample should be obtained at the 30-day SFU.

Further details on sample processing, handling, and shipment are provided in the Laboratory Manual.

26.10 CCI

CCI

26.10.1 Collection of Archival Tumour Samples

All participants in Part A (dose setting) must consent to and provide a sample of their archival tumour obtained within 24 months before the first dose of treatment. The archival tumour biopsy sample formalin-fixed paraffin embedded (FFPE) tumour block should be provided with sufficient material to produce 20 slides (minimum 15 slides acceptable), or where an archival tumour biopsy FFPE tumour block is unavailable, archival tumour biopsy FFPE unstained slides (20 unstained slides preferable, minimum 15 slides acceptable) must be provided. Archival tissues must have been obtained as a core biopsy and meet the specified criteria detailed in the Laboratory Manual. Associated pathology report(s) for archival tissue samples must be obtained at Screening for all participants enrolled into the study.

If archival material is unavailable or unsuitable for use, participants must consent to and undergo a tumour biopsy during the Screening period. A new biopsy is strongly encouraged and preferred over an archival sample. A participant will be enrolled based on a prior pathology report.

Further details on sample processing, handling, and shipment are provided in the Laboratory Manual.

26.10.2 Collection of Tumour Biopsy Samples

Participants in Part A who are unable to provide archival tumour specimens obtained within 24 months before the first dose of treatment will be asked to undergo a tumour biopsy at Screening. A new biopsy is strongly encouraged and preferred over an archival sample.

This sample will be used to evaluate potential participant selection biomarkers through methods such as, but not limited to, immunohistochemistry (eg, baseline expression of Bfl1), gene expression analysis, and DNA sequencing. A recent biopsy that was taken as part of SoC prior to screening consent for this study is acceptable if no treatment was administered between the biopsy and the first dose of study treatment, and the biopsy was taken within 60 days prior to receiving the first dose.

All participants are also encouraged to consent to an additional optional tumour biopsy at disease progression. The optional disease progression sample may be taken at the 30-day SFU visit if not collected previously (see Section 26.10.5).

The tumour biopsy procedure will be performed by core needle, under radiological guidance, or surgically if the site of disease is superficial and palpable or visible (eg, palpable lymph node). Tumour biopsies should be preferentially obtained from tumour tissues that are safely accessible, as determined by the Investigator, and are not obtained from sites that require significant risk procedures. Participants will undergo 6 core image-guided needle biopsies. It is mandated that the core biopsy be removed directly from the tumour in situ and not cored from a surgically removed tumour. This is to ensure the best possible quality of the biopsy, as the blood/nutrient supply to the tumour is not disrupted prior to biopsy collection. Fine-needle aspirate specimens are not acceptable. Failure to obtain sufficient tumour sample after making best efforts to biopsy the tumour will not be considered a protocol deviation.

Sites should confirm the adequacy of tumour biopsy material at the time of the procedure. The exact time that the biopsy was taken should be clearly noted in the associated documentation. For mandatory and optional biopsy participants, the associated pathology report(s) for fresh tumour samples will be required at Screening and requested on treatment for all participants enrolled into the study.

Further details on sample processing, handling, and shipment are provided in the Laboratory Manual.

All participants are also encouraged to consent to an additional optional tumour biopsy at disease progression. The optional disease progression sample may be taken at the 30-day SFU visit if not collected previously (see Section 26.10.5.1).

26.10.3 Collection of Bone Marrow

For all participants, when bone marrow biopsy and aspirate samples are collected for local standard disease profiling (refer to Section 26.4.3 for timepoints), CCI [redacted]

CCI [redacted]

Instructions on sample collection, labelling, processing, storage, and shipping will be provided in the laboratory manual.

26.10.4 Other Study Related CCI Research

26.10.4.1 CCI Sample for CCI Isolation

Per local regulations, a mandatory CCI sample for CCI will be collected from all participants in this module. CCI [redacted] The sample should be collected from participants before receiving study treatment.

Details on sample processing, handling, and shipment are provided in the Laboratory Manual.

26.10.5 Collection of Optional CCI Samples

Collection of optional samples for CCI research is also part of this study as specified in the SoA (Section 19.2) and is subject to agreement to optional consent.

26.10.5.1 Optional Tumour Biopsy at Disease Progression

For participants who consent to the optional tumour biopsy, a biopsy will be taken at disease progression. The disease progression sample may be taken at the SFU visit if not collected previously.

Details on sample processing, handling, shipment, and storage are provided in the Laboratory Manual.

26.11 Optional Genomics Initiative Sample

Collection of optional saliva samples for genomics initiative research is also part of this study as specified in the SoA (Section 19.2) and is subject to agreement in the ICF addendum.

A saliva sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is

optional. Participants who do not wish to participate in the genetic research may still participate in the study.

The saliva sample for exploratory genetic research will be obtained from the participants before the first dose of IP. If for any reason the sample is not taken before dosing it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

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

For storage and destruction of genetic samples, please refer to Appendix D.

26.12 Medical Resource Utilisation and Health Economics

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

26.13 Important Medical Procedures to be Followed by the Investigator

26.13.1 Medical Emergencies and Contacts

The principal Investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, please refer to Section 8.2.10.**

In the case of a medical emergency the Investigator may contact the Medical Monitor. If the Medical Monitor is not available, contact the Medical Scientist.

27 STATISTICAL CONSIDERATIONS – MODULE 2

27.1 Statistical Hypotheses

No hypotheses are planned to be tested.

27.2 Sample Size Determination

Approximately 12 participants will be treated with AZD4573 ± acalabrutinib in this module.

The primary objective of Part A will be to assess safety and confirm the RP2D of AZD4573 monotherapy in MCL participants and assess the safety and tolerability of AZD4573 in combination with acalabrutinib in participants administered AZD4573 monotherapy. Anti-tumour activity will also be explored in Part A.

Even though the sample size is not based on the expected ORR, the following examples (Table 42) give an indication of the information obtained with response data from n=12 participants in Period 1 and n=11, 10, 9, 8, 7, and 6 participants in Period 2. For example, for CCI [redacted]

Table 42 CCI [redacted]

CCI [redacted]

CCI

[redacted]

Note: Probabilities are calculated based on the CCI

[redacted]

Abbreviations: ORR = objective response rate; Pr = probability.

27.3 Populations for Analyses

The analysis of data will be based on different subsets according to the purpose of the analysis.

Analysis sets are presented in Table 43.

Table 43 Analysis Sets -Module 2

Analysis Set	Definition
Enrolled	All participants who sign the ICF.
Safety	All participants who received any amount of AZD4573 and/or acalabrutinib.
Pharmacokinetics	All dosed participants with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK.
Response evaluable	Participants dosed with AZD4573 or acalabrutinib with a baseline tumour assessment.
Interim response evaluable	Participants 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 participants who received any amount of study intervention.

Abbreviations: ICF = Informed Consent Form; ITT = intent-to-treat; PK = pharmacokinetics.

27.4 Statistical Analyses

The SAP will be finalised prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints, as defined in Section 21 (Table 26).

27.4.1 General Considerations

Descriptive statistics (including means, standard deviations, medians for continuous variables and proportions, and CIs for discrete variables) will be used to summarise data by treatment period as appropriate. Kaplan-Meier methods will be used to estimate DoR, PFS, and OS; corresponding quartiles (including the median) and 3-month and 6-month and 12-month rates may be presented as appropriate.

27.4.2 Demographics, Baseline Characteristics, and Study Status

Characteristics of the participants, including medical history, disease characteristics at baseline, and previous and concomitant treatments (coded according to WHODRUG) will be listed for each participant and summarised by treatment period where appropriate.

Reasons for discontinuation of study treatment and withdrawal from study will be listed including the study day of treatment discontinuation/study withdrawal and will be summarised by treatment period if appropriate.

27.4.3 Exposure

Exposure to AZD4573 and acalabrutinib will be listed for all participants.

Exposure amounts, durations, and dose modifications and interruptions/delays will be summarised by study drug and treatment period, separately for Cycle 1 (including intra-patient ramp up) and for other treatment cycles.

27.4.4 Safety

Safety and tolerability will be assessed in terms of frequency and types of AEs, and changes in laboratory data, vital signs, and ECG, when compared to baseline.

Adverse events will be listed individually by participant and treatment period, separately for Cycle 1 and for other treatment cycles. The number of participants experiencing each AE will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade, with the exception of clinical TLS which will use both CTCAE grade and Cairo-Bishop criteria (Howard modification); see Appendix F). The number and percentage of participants with AEs in different categories (eg, causally related and CTCAE Grade ≥ 3) will be summarised by treatment period, and events in each category will be further summarised by MedDRA system organ class and preferred term. SAEs will be summarised separately if a sufficient number occur.

AE summary tables will include only treatment-emergent AEs. AEs will be defined as treatment-emergent if they have an onset or worsen (by Investigator report of a change in intensity/severity), during the study treatment until 30 days from the last dose of any study intervention, but prior to subsequent cancer therapy. AEs occurring outside this period will be flagged in listings.

Haematology, clinical chemistry, coagulation, vital signs, ECG data, and other laboratory values will be listed individually by participant and suitably summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated.

Details of any deaths will be listed for all participants.

Graphical presentations of safety data will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time,

concentration, or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared to baseline level.

ECG Changes

QTc will be calculated using Fridericia's formula.

Creatinine Clearance

Estimated creatinine clearance will be calculated using the Cockcroft and Gault formula.

Other Significant Adverse Events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation of study treatment. Based on the expert's judgement, AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory values, vital signs, ECGs, and other safety assessments will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

27.4.5 Efficacy

Tumour response data will be listed and summarised by treatment period, using the standard response criteria as defined in Section 26.4.1.

For Part A participants, all efficacy endpoints are exploratory. Planned analysis of exploratory endpoints will be outlined in the SAP.

27.4.5.1 Objective Response Rate and Proportion of Participants with Complete Response

The ORR is defined as the proportion of participants who achieve either a CR or PR, according to the Lugano Response Criteria for Non-Hodgkin's Lymphoma (Cheson et al 2014). Data obtained from first dose of study treatment up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who discontinue treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

ORR and proportion of participants with CR will be presented with corresponding 80% and 95% two-sided CIs.

27.4.5.2 Time to Response (TTR)

Time to response is defined as the time from the first dose of study treatment to the first objective response observed for participants who achieved a CR or PR. The date of first documented response should coincide with that used for the DoR endpoint. TTR will not be defined for those participants who do not have a documented response. TTR data will be listed and summarised.

27.4.5.3 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. KM curves and estimates may be presented, if appropriate.

27.4.5.4 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 participant withdraws from therapy or receives another anti-cancer therapy prior to progression. Participants who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable disease assessment. However, if the participant progresses or dies immediately after 2 or more consecutive missed visits, the participant is censored at the time of the latest evaluable disease assessment prior to the 2 missed visits.

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

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

- Date of progression will be determined, based on the earliest of the dates of the component that triggered the progression.
- When censoring a participant for PFS, the participant will be censored at the latest of the dates contributing to a particular overall visit assessment.

Kaplan-Meier plots will be provided.

27.4.5.5 Overall Survival (OS)

Overall survival is defined as the time from first dose until date of death from any cause. Participants 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. Participants known to be alive or dead after the data cut-off date will be censored at the data cut-off date. Participants who are

lost to follow-up will be censored at the date of the participant is last known to have been alive. KM curves and estimates may be presented, if appropriate.

27.4.6 Pharmacokinetics

Pharmacokinetic results are a secondary objective for Part A.

Plasma concentrations of AZD4573 plus acalabrutinib and its metabolite ACP-5862 will be summarised by nominal sample time. Plasma concentrations and derived PK parameters will be summarised by treatment period. Plasma concentrations and the derived PK parameters at each time point will be summarised according to treatment by the following summary statistics:

- The geometric mean (gmean)
- Coefficient of variation (CV)
- Gmean ± standard deviation
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum
- Median
- Maximum
- Number of observations

The PK data for AZD4573, acalabrutinib and its metabolite ACP-5862 will also be displayed graphically. Displays will include plasma concentration participant profiles (on the linear and log-scale) versus time and gmean concentration (± standard deviation) versus time, stratified by dose.

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

Derived PK parameters to be determined include Cmax, AUC0-t, AUClast, AUC0-inf, tmax, and t1/2.

Additional PK parameters may be determined.

27.5 Safety Review Committee – Module 2

An SRC, which includes the principal investigators, is tasked with the review of the available safety data (AEs and available pharmacokinetics/pharmacodynamics [PKPD]

data) for AZD4573 alone or in combination with acalabrutinib. All decisions made by the SRC will be documented in writing in the form of meeting minutes.

The SRC will meet during Module 2, Part A after the first 6 participants have completed Period 1, Cycle 1, and again after the first 6 participants entering Period 2 have completed Cycle 1. The AZD4573 monotherapy RP2D established in DLBCL (12 mg once weekly; study D8230C00001) will be evaluated in MCL participants (Period 1), and safety and tolerability compared with the known safety profile in DLBCL participants to confirm the RP2D in the MCL population. The AZD4573 + acalabrutinib combination RP2D established in participants with DLBCL from Module 1 will be evaluated in MCL participants (Period 2) after receiving AZD4573 monotherapy RP2D in Period 1.

A proposed interpretation of the dose confirmation of the AZD4573 monotherapy RP2D and assessment of the AZD4573 + acalabrutinib RP2D safety data will be presented to the SRC, who will provide their recommendations on the continued development of AZD4573 monotherapy and/or in combination with acalabrutinib in MCL participants. This process will be further described in the SRC Charter.

The SRC will continue to monitor safety and tolerability data for all participants in Part A as described in the SRC Charter.

Please refer to Appendix A 5 and the SRC Charter for further information on the SRC.

The decisions and decision-making of the SRC will be documented and provided to the investigators.

28 REFERENCES

Adelman and Lis 2012
Adelman K, Lis JT. Promoter-proximal pausing of RNA polymerase II: emerging roles in metazoans. Nat Rev Genet. 2012;13(10):720-31.

Awan et al 2019
Awan FT, Schuh A, Brown JR, Furman RR, Pagel JM, Hillmen P, et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. Blood Adv. 2019;3(9):1553-62.

Baiocchi et al 2010
Baiocchi RA, Flynn JM, Jones JA, Blum KA, Hofmeister CC, Poon J et al. Early evidence of anti-lymphoma activity of the cyclin-dependent kinase inhibitor dinaciclib (SCH 727965) in heavily pre-treated low grade lymphoma and diffuse large-cell lymphoma patients. Blood. 2010;116(21):3966.

Balko et al 2014
Balko JM, Giltnane JM, Wang K, Schwarz LJ, Young CD, Cook RS, et al. Molecular profiling of the residual disease of triple-negative breast cancer after neoadjuvant chemotherapy identifies actionable therapeutic targets. Cancer Discov. 2014;4:232-45.

Beroukhim et al 2010
Beroukhim R, Mermel CH, Porter D, Wei G, Raychaudhuri S, Donovan J, et al. The landscape of somatic copy-number alterations across human cancers. Nature. 2010;463:899-905.

Boiko et al 2020
Boiko S, Proia TA, San Martin M, Gregory G, Wu MM, Aryal NK et al. Targeting Bfl-1 via acute CDK9 inhibition overcomes intrinsic BH3 mimetic resistance in lymphomas. Blood. 2021;137:2947-57.

Booher et al 2014
Booher RN, Hatch H, Dolinski BM, Nguyen T, Harmonay L, Al-Assaad AS, et al. MCL-1 and BCL-xL levels in solid tumors are predictive of dinaciclib-induced apoptosis. PLoS One. 2014;9(10):e108371.

Bywater et al 2013
Bywater MJ, Pearson RB, McArthur GA, Hannan RD. Dysregulation of the basal RNA polymerase transcription apparatus in cancer. Nat Rev Cancer. 2013;13(5):299-314.

Calquence United States Prescribing Information
Revised November 2019; Reference ID: 4523127.

Cheson et al 2012
Cheson BD, Byrd JC, Rai KR, Kay NE, O'Brien SM, Flinn IW, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol 2012;30:2820-22.

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.

Cho-Vega et al 2004
Cho-Vega JH, Rassidakis GZ, Admirand JH, Oyazaro M, Ramalingam P, Paraguya A, et al. MCL-1 expression in B-cell non-Hodgkin's lymphomas. Hum Pathol. 2004;35(9):1095-1100.

Cidado et al 2020
Cidado J, Boiko S, Proia T, Ferguson D, Criscione SW, San Martin M, et al. AZD4573 is a highly selective CDK9 inhibitor that suppresses MCL-1 and induces apoptosis in hematologic cancer cells. Clin Cancer Res. 2020;26(4):922-34.

Ciriello et al 2013
Ciriello G, Miller ML, Aksoy BA, Senbabaoglu Y, Schultz N, Sander C. Emerging landscape of oncogenic signatures across human cancers. Nat Genet. 2013;45:1127-33.

Coiffier et al 2008
Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26(16):2767-78.

Davis et al 2010
Davis RE, Ngo VN, Lenz G, Tolar P, Young RM, Romesser PB, et al. Chronic active B-cell-receptor signaling in diffuse large B-cell lymphoma. Nature. 2010;463(7277):88-92.

Deng 2017a
Deng J. How to unleash mitochondrial apoptotic blockades to kill cancers? Acta Pharmaceutica Sinica B. 2017:7(1):18-26.

Deng et al 2017b
Deng J, Isik E, Fernandes SM, Brown JR, Letai A, Davids MS. Bruton's tyrosine kinase inhibition increases BCL-2 dependence and enhances sensitivity to venetoclax in chronic lymphocytic leukemia. Leukemia. 2017;31(10):2075-84.

Dreyling et al 2018
Dreyling M, Aurer I, Cortelazzo S, Hermine O, Hess G, Jerkeman M, et al. Treatment for patients with relapsed/refractory mantle cell lymphoma: European-based recommendations. Leuk Lymphoma. 2018;59:1814-28.

Denlinger et al 2018
Denlinger NM, Epperla N, William BM. Management of relapsed/refractory marginal zone lymphoma: focus on ibrutinib. Cancer Manag Res. 2018;10:615-24.

Dyer et al 2018
Dyer MJ, De Vos S, Ruan J, Flowers C, Maddocks K, Rule S, et al. Acalabrutinib monotherapy in patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). J of Clin Oncol. 2018;36(15 suppl):7547.

FDA 2017
FDA Guidance for Industry (Draft, 2017). In vitro metabolism and transporter-mediated drug-drug interaction studies. https://www.fda.gov/media/108130/download (Accessed 06 April 2021).

Flynn et al 2015
Flynn J, Jones J, Johnson AJ, Andritsos L, Maddocks K, Jaglowski S, et al. Dinaciclib is a novel cyclin-dependent kinase inhibitor with significant clinical activity in relapsed and refractory chronic lymphocytic leukemia. Leukemia. 2015;29:1524-29.

Gilchrist et al 2010
Gilchrist DA, Dos Santos G, Fargo DC, Xie B, Gao Y, Li L, et al. Pausing of RNA polymerase II disrupts DNA-specified nucleosome organization to enable precise gene regulation. Cell. 2010;143:540-51.

Glaser et al 2012
Glaser SP, Lee EF, Trounson E, Bouillet P, Wei A, Fairlie WD, et al. Anti-apoptotic Mcl-1 is essential for the development and sustained growth of acute myeloid leukemia. Genes Dev. 2012;26:120-25.

Gojo et al 2013
Gojo I, Sadowska M, Walker A, Feldman EJ, Iyer SP, Baer MR, et al. Clinical and laboratory studies of the novel cyclin-dependent-kinase inhibitor dinaciclib (SCH 727965) in acute leukaemias. Cancer Chemother Pharmacol. 2013;72 897-908.

Gomez-Bougie et al 2007
Gomez-Bougie P, Wuilleme-Toumi S, Menoret E, Trichet V, Robillard N, Philippe M, et al. Noxa up-regulation and Mcl-1 cleavage are associated to apoptosis induction by bortezomib in multiple myeloma. Cancer Res. 2007;67:5418-24.

Goy and Kahl 2011
Goy A and Kahl B. Mantle cell lymphoma: the promise of new treatment options. Crit Rev Oncol Hematol. 2011;80:69-86.

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.

Hallek et al 2008
Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111:5446-56.

Hann and Eisenman 1984
Hann SR, Eisenman RN. Proteins encoded by the human c-myc oncogene: differential expression in neoplastic cells. Mol Cell Biol. 1984;4:2486-97.

Harrington et al 2016
Harrington BK, Gardner HL, Izumi R, Hamdy A, Rothbaum W, Coombes KR, et al. Preclinical evaluation of the novel BTK inhibitor acalabrutinib in canine models of B-cell non-Hodgkin lymphoma. PLoS One. 2016;11(7):e0159607.

Hernandez-Ilizaliturri et al 2011
Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, Pileri SA, Malik F, Macon WR, et al. Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell–like than in germinal center B-cell–like phenotype. Cancer. 2011;117(22):5058-66.

Howard et al 2016
Howard SC, Trifilio S, Gregory TK, Baxter N, McBride A. Tumor lysis syndrome in the era of novel and targeted agents in patients with hematologic malignancies: a systematic review. Ann Hematol. 2016;95(4):563-73.

Howard et al 2011
Howard SC, Jones DP, Pui C-H. The tumor lysis syndrome. N Engl J Med. 2011;364:1844-54.

Jones et al 2015
Jones GL, Will A, Jackson GH, Webb NJ, Rule S. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. Br J Haematol. 2015; 169(5):661-71.

Khoury et al 2003
Khoury JD, Medeiros LJ, Rassidakis GZ, McDonnell TJ, Abruzzo LV, Lai R. Expression of Mcl-1 in mantle cell lymphoma is associated with high-grade morphology, a high proliferative state, and p53 overexpression. J Pathol. 2003;199(1):90-7.

Kouroukis et al 2003
Kouroukis CT, Belch A, Crump M, Eisenhauer E, Gascoyne RD, Meyer R et al. Flavopiridol in untreated or relapsed mantle cell lymphoma: results of a phase II study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2003;21(9):1740-5.

Krystof et al 2012
Krystof V, Baumli S, Furst R. Perspective of cyclin-dependent kinase 9 (CDK9) as a drug target. Curr Pharm Des. 2012;18:2883-90.

Kumar et al 2015
Kumar SK, LaPlant B, Chng WJ, Zonder J, Callander N, Fonseca R, et al. Dinaciclib, a novel CDK inhibitor, demonstrates encouraging single-agent activity in patients with relapsed multiple myeloma. Blood. 2015;125:443-8.

Lue et al 2020
Lue JK, O'Connor OA, Bertoni F. Targeting pathogenic mechanisms in marginal zone lymphoma: from concepts and beyond. Ann Lymphoma. 2020;4(7):no pages listed.

Lim and Kaldis 2013
Lim S, Kaldis P. Cdks, cyclins and CKIs: roles beyond cell cycle regulation. Development. 2013;140:3079-93.

Malumbres 2014
Malumbres M. Cyclin-dependent kinases. Genome Biol. 2014;15:122.

Morales and Giordano 2016
Morales F, Giordano A. Overview of CDK9 as a target in cancer research. Cell Cycle. 2016;15:519-27.

Morschhauser et al 2014
Morschhauser F, Flinn I, Advani RH, Diefenbach CS, Kolibaba K, Press OW, et al. Updated results of a phase II randomized study (ROMULUS) of polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed/refractory non-Hodgkin lymphoma. Blood. 2014;124(21):4457.

NCCN 2021
NCNN Guidelines. B-cell lymphomas. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1480 (Accessed 10 June 2021).

Ni Chonghaile et al 2011
Ni Chonghaile T, Sarosiek KA, Vo TT, Ryan JA, Tammareddi A, Moore Vdel G, et al. Pretreatment mitochondrial priming correlates with clinical response to cytotoxic chemotherapy. Science. 2011;334(6059):1129-33.

Nowakowski et al 2019
Nowakowski GS, Feldman T, Rimsza LM, Westin JR, Witzig TE, Zinzani PL. Integrating precision medicine through evaluation of cell of origin in treatment planning for diffuse large B-cell lymphoma. Blood Cancer J. 2019;9(6):48.

Noy et al 2017
Noy A, de Vos S, Thieblemont C, Martin P, Flowers CR, Morschhauser F, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Blood. 2017;129(16):2224-32.

Parry et al 2010
Parry D, Guzi T, Shanahan F, Davis N, Prabhavalkar D, Wiswell D, et al. Dinaciclib (SCH 727965), a novel and potent cyclin-dependent kinase inhibitor. Mol Cancer Ther. 2010;9:2344-53.

Rahaman et al 2016
Rahaman MH, Kumarasiri M, Mekonnen LB, Yu M, Diab S, Albrecht H, et al. Targeting CDK9: a promising therapeutic opportunity in prostate cancer. Endocr Relat Cancer. 2016;23:T211-26.

Sanso and Fisher 2013
Sanso M, Fisher RP. Pause, play, repeat: CDKs push RNAP II's buttons. Transcription. 2013;4:146-52.

Sasi et al 2019
Sasi BK, Martines C, Xerxa E, Porro F, Kalkan H, Fazio R, et al. Inhibition of SYK or BTK augments venetoclax sensitivity in SHP1-negative/BCL-2-positive diffuse large B-cell lymphoma. Leukemia. 2019;33(10):2416-28.

Silkenstedt et al 2021
Silkenstedt E, Linton K, Dreyling M. Mantle cell lymphoma – advances in molecular biology, prognostication and treatment approaches. Br J Haematol. Epub 2021 Mar.

Soucek et al 2013
Soucek. L, Whitfield JR, Sodir NM, Masso-Valles D, Serrano E, Karnezis AN, et al. Inhibition of Myc family proteins eradicates KRas-driven lung cancer in mice. Genes Dev. 2013;27:504-13.

Stewart et al 2010
Stewart DP, Koss B, Bathina M, Perciavalle RM, Bisanz K, Opferman JT. Ubiquitin-independent degradation of antiapoptotic MCL-1. Mol Cell Biol. 2010;30:3099-3110.

Van den Neste et al 2016
Van den Neste E, Schmitz N, Mounier N, Gill D, Linch D, Trneny M, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant. 2016;51(1):51-7.

Van den Neste et al 2017
Van den Neste E, Schmitz N, Mounier N, Gill D, Linch D, Trneny M, et al. Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. Bone Marrow Transplant. 2017;52(2):216-21.

Varadarajan et al 2015
Varadarajan S, Poornima P, Milani M, Gowda K, Amin S, Wang H-G, et al. Maritoclax and dinaciclib inhibit MCL-1 activity and induce apoptosis in both a MCL-1-dependent and independent manner. Oncotarget. 2015;6:12668-81.

Wang et al 2018
Wang M, Rule S, Zinzani PL, Goy A, Casasnovas O, Smith SD, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet 2018;391:659-67.

Wang et al 2020
Wang M, Rule S, Zinzani PL, Goy A, Casasnovas O. Smith SD, et al. Acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study [abstract]. Proceedings of the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition; 2020 Dec 06; Online: abstract 2040.

Wilson et al 2015
Wilson WH, Young RM, Schmitz R, Yang Y, Pittaluga S, Wright G, et al. Targeting B-cell-receptor signaling with ibrutinib in diffuse large B-cell lymphoma. Nat Med. 2015;21(8):922-6.

Witzig et al 2011
Witzig TE, Reeder CB, LaPlant BR, Gupta M, Johnston PB, Micallef IN, et al. A phase II trial of the oral mTOR inhibitor everolimus in relapsed aggressive lymphoma. Leukemia. 2011;25(2):341-7.

Yang et al 1996
Yang T, Buchan HL, Townsend KJ, Craig RW. MCL-1, a member of the BCL-2 family, is induced rapidly in response to signals for cell differentiation or death, but not to signals for cell proliferation. J Cell Physiol. 1996;166(3):523-36.

Zhou et al 2001
Zhou P, Levy NB, Xie H, Qian L, Lee CY, Gascoyne RD, Craig RW. MCL1 transgenic mice exhibit a high incidence of B-cell lymphoma manifested as a spectrum of histologic subtypes. Blood. 2001;97(12):3902-9.

Zucca et al 2020
Zucca E, Arcaini L, Buske C, Johnson PW, Ponzoni M, Raderer M, et al. Marginal zone lymphomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(1):17-29.

29 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organisation (CRO) but the accountability remains with AstraZeneca.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority IRB/IEC, and investigators.
- For all studies except those utilising medical devices Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the [Investigator's Brochure or state other

documents] and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the AstraZeneca Study Team with sufficient, accurate financial information as requested to allow the AstraZeneca Study Team to submit complete and accurate financial certification or disclosure statements to the appropriate Regulatory Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

A 3 Informed Consent Process

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

To participate in the optional Genomics Initiative component of the study the participant should sign and date the consent form for the main study and, as applicable, a separate consent form for the Genomics Initiative components of the study.

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only;

participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from Regulatory Authorities.

A 5 Committees Structure

The detailed remit and functioning of the SRC will be defined in the SRC Charter.

The SRC Charter for this study will define the exact membership and who should be present for decisions to be made.

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

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

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

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source data may include, but are not limited to: medical history and physical examination notes, hospital discharge summary, autopsy report (when available), results of relevant diagnostic tests completed.
- All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

- A digital copy of all imaging scans should be stored as source documents.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants in the first module.

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/IECs, the Regulatory Authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

A 11 Study Protocol Requirements During the 2019-Novel Corona Virus Outbreak (COVID-19)

Benefit/risk pertaining to conduct of trial during COVID-19 pandemic

Respiratory viral infections pose a particular threat to patients with haematological malignancies due to their increased tendency in this population to progress to severe lower respiratory tract infections (LRTIs) (Martino et al 2003, Dignan et al 2016) and their association with bacterial/fungal superinfections (Hermann et al 2017). In the case of COVID-19, it is not yet clear whether cancer patients have a higher risk of COVID-19 or of more severe outcomes (Liang et al 2020, Xia et al 2020). It is known, however, that cancer patients are more likely to have factors that predispose them to a poor prognosis with COVID-19, such as advanced age, hypertension, and diabetes (Zhou et al 2020). Additionally, cancer patients may have an increased risk of exposure to the virus due to hospital visits for treatment, as was reported in a retrospective cohort study of 28 COVID-19-infected cancer patients from 3 hospitals in Wuhan, China, in which a third of patients (28.6%; N = 8) were suspected to have acquired the infection by hospital-associated transmission (Zhang et al 2020). In terms of mortality risk of COVID-19 in patients with haematological malignancy, data are limited but preliminary experience from Italy suggests that rates may be as high as 20% (von Lilienfeld-Toal et al 2020).

This trial will enrol participants with selected haematological malignancies who have relapsed after, or are refractory to prior standard therapy, and for whom there is no other standard therapy available. The prognosis for these patients is poor: for example, the median OS for patients with r/r DLBCL proposed to be enrolled in Module 1 is approximately 6 months (Crump et al 2017). These patients are also at increased risk of disease-related cytopenias and severe opportunistic infections (Safdar and Armstrong 2001). Thus, although there may be risks to patients associated with increased opportunity for exposure to SARS-CoV-2 during trial visits, this is offset by the benefit that patients may receive by potential control of their disease.

In accordance with FDA and European Medicines Agency (EMA) guidelines (EMA-CTFG-EC 2020; FDA 2021), a risk assessment will be conducted in collaboration with investigators for each site and participant prior to site initiation/participant enrolment and on an ongoing basis throughout the trial to assess whether additional measures may be necessary to ensure participant safety and data validity. Measures may include postponement of study start on a global, country or site level or suspension of recruitment of participants in locations with an increased risk of COVID-19 related disruption. Given

the proposed dosing regimen for AZD4573 requiring weekly administration in a hospital setting there is limited opportunity to reduce participant contact with sites; however, additional guidance on alternative means of obtaining reconsent to avoid unnecessary study visits is provided below (as a supplement to the standard consent procedures in Appendix A 3). Any deviations to the protocol necessary to safeguard participant safety or data validity as a result of COVID-19 related disruption will be recorded and any permanent changes requiring an amendment to the protocol will be communicated to Regulatory Authorities and IRBs / ECs in line with relevant local guidance and procedures (see Appendix A 1).

AstraZeneca recommends administering non-live inactivated vaccines 72 hours prior to administration of the first dose of any IP to avoid biases in the interpretation of safety data due to the potential overlap of vaccine-related AEs with IP AEs.

Potential Changes to Informed Consent during the COVID-19 outbreak

General Principles

- The rights, safety, and wellbeing of the trial participants are the most important considerations and should prevail over interests of science and society. All informed consent activities must follow ICH GCP, the CSP, and local laws, regulations and guidance. Prospective protocol waivers with respect to enrolment remain unacceptable. Participants should not be included in studies without written informed consent according to national laws and regulations and proper eligibility assessment.
- The reconsent process described in this appendix must be adopted only at sites/countries affected by the COVID-19 outbreak where reaching the site means placing the trial participant under unnecessary risk. The described process does not overrule local laws, regulations and guidance; where differences arise, the latter must be followed.
- If the need for re-consenting trial participants arises, visiting the Investigator sites for the sole purpose of obtaining reconsent should be avoided.
- Any validated and secure electronic system already used in the trial for obtaining informed consent can be used as per usual practice and if in compliance with local regulations.

Process for reconsent of trial participants at sites affected by the COVID-19 outbreak

Before reconsent is obtained, the approved updated participant information sheet and consent form should be provided to trial participants by email. If the trial participant is not able to receive e-mails, courier or mail should be used.

- Verbal consent via phone or teleconference is allowed.
- If possible, verbal consent should be supplemented with email confirmation. The Investigator should emphasize that trial participants should only use email to confirm their ICF consent and that the participant should not include any sensitive personal identifier (eg, date of birth, social security number etc.) or medical information including AEs.
- Please note: Trial participants should not sign the document at home after giving verbal consent. The phone call or teleconference should be informative. The document will be signed and filed with the participant's source data once the trial participant is able to attend the site. Under no circumstances should the trial participant scan and send the document back via email.
  - Verbal consent and print-out of the email confirmation (if available and once possible) must be documented by the Investigator or delegate (if applicable) in the trial participant's medical records:
  - Documentation should include details on when the contact took place, the reason why the trial participant could not reach the site, any important details of the consenting call/concerns raised, any questions raised (especially on safety measures) by the trial participant and that these were answered satisfactorily by the site consenting party.
- At the earliest possible occasion, consent must be documented via standard consent process. This would not apply if the trial participant is lost to follow-up, dies or study ends before the COVID-19 outbreak is over. In this case the reason why the trial participant did not sign the document in person has to be documented in the trial participant's medical records.

Courier Use

A courier may be used

- when participants do not have access to email.
- to deliver study drug to the participant's home.
- to pick up biological samples from the participant's home.

References

Crump et al 2017
Crump M, Neelapu SS, Farooq U, Van den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800–08.

Dignan et al 2016
Dignan FL, Clark A, Aitken C, Gilleece M, Jayakar V, Krishnamurthy P, et al. BCSH/BSBMT/UK clinical virology network guideline: diagnosis and management of common respiratory viral infections in patients undergoing treatment for haematological malignancies or stem cell transplantation. Br J Haematol. 2016;173(3):380-93.

EMA-CTFG-EC 2020
European Medicines Agency (EMA), Clinical Trials Facilitation and Coordination Group (CTFG), European Commission (EC). Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic, Version 2, 27 March 2020. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. Accessed 16 April 2020.

FDA 2021
US Food and Drug Administration (FDA). Guidance on conduct of clinical trials of medical products during COVID-19 public health emergency, March 2020 (updated January 2021). https://www.fda.gov/media/136238/download. Accessed 11 June 2021.

Hermann et al 2017
Hermann B, Lehners N, Brodhun M, Boden K, Hochhaus A, Kochanek M, et al. Influenza virus infections in patients with malignancies - characteristics and outcome of the season 2014/15. A survey conducted by the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Medical Oncology (DGHO). Eur J Clin Microbiol Infect Dis. 2017;36(3):565-73.

Liang et al 2020
Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7.

Martino et al 2003
Martino R, Rámila E, Rabella N, Muñoz JM, Peyret M, Portos JM, et al. Respiratory virus infections in adults with hematologic malignancies: a prospective study. Clin Infect Dis. 2003;36(1):1-8.

Safdar and Armstrong 2001
Safdar A, Armstrong D. Infectious morbidity in critically ill patients with cancer. Crit Care Clin. 2001;17(3):531-70.

von Lilienfeld-Toal et al 2020
von Lilienfeld-Toal M, Vehreschild JJ, Cornely O, Pagano L, Compagno F, EHA Infectious Disease Scientific Working Group, et al. Frequently asked questions regarding SARS-CoV2 in cancer patients: recommendations for clinicians caring for patients with

malignant diseases. 25 March 2020. https://ehaweb.org/assets/Uploads/01-EHA-SWB-Infect-Manuscript-FAQ-COVID19-25032020.pdf. Accessed 16 April 2020.

Xia et al 2020
Xia Y, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for patients with cancer. Lancet Oncol. 2020;21(4):e180.

Zhang et al 2020
Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol. 2020; 26. pii: S0923-7534(20)36383-3.

Zhou et al 2020
Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An adverse event (AE) is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

B 2 Definitions of Serious Adverse Event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events for **malignant tumours** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **Non-Serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as Serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as Non-Serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (ie, it is *not* the tumour for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B-cell CLL into DLBCL) should not be considered a new malignant tumour.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity rating scale:

mild (awareness of sign or symptom, but easily tolerated)

moderate (discomfort sufficient to cause interference with normal activities)

severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

The grading scales found in the revised National Cancer Institute CTCAE latest version will be utilised for all events with an assigned CTCAE grading, with the exception of TLS which will use both CTCAE grade and Howard modification of Cairo-Bishop criteria (see Appendix F). For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study-site staff or participant.

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion

- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding Interactive Voice Response System [IVRS]/Interactive Web Response System [IWRS] errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or SoC medication in open-label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their life cycle.

The Investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

C 2 Withdrawal of Informed Consent for Donated biological samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.

Category A pathogens are eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.

Appendix D Optional Genomics Initiative Saliva Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a saliva sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on AZD4573 continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic Research Plan and Procedures

Selection of genetic research population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant.
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection.
  - Healthy Volunteers and paediatric patient samples will not be collected for the Genomics Initiative.

Withdrawal of consent for genetic research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main Clinical Study Protocol.

Collection of samples for genetic research

- The saliva sample for this genetic research will be obtained from the patients before the first dose of IP. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn before the first dose of IP, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and storage of DNA samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code (DNA number) will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).
- The link between the participant enrolment number and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed consent

- The genetic component of this study is optional, and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The principal Investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant data protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, or general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.
- AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-

related research purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.

- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.
- The results of the Genomics Initiative research will be reported separately and will not form part of the Clinical Study Report.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

Specific guidance on managing liver anomalies can be found in the Dose Modification section of each module in the Clinical Study Protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated total bilirubin (TBL) from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator will participate, together with the Medical Monitor, in review and assessment of PHL events to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) $\geq 3 \times$ Upper Limit of Normal (ULN) **together with** TBL $\geq 2 \times$ ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Local laboratories being used:

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative (Medical Monitor)
- Determine whether the participant meets PHL criteria (see Section E 1 Definitions within this appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria Not Met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (see Section E 6)
- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE; serious criteria 'Important Medical Event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
    - Events that meet PHL criteria will be reported as an SAE with the reported term "Potential Hy's Law" ONLY if:
        - The ALT and bilirubin elevations did not improve by Day 3 from Start of Infusion (SOI) or resolve back to baseline by Day 5, and/or
        - INR ≥1.5 x ULN (or an absolute increase of 0.3 x baseline if elevated at baseline) of any duration at the time of ALT elevation, and/or
        - Was accompanied by clinical symptoms of liver impairment including fatigue, nausea, vomiting, abdominal pain, and/or
        - Required hospitalization for monitoring or treatment, or was considered clinically relevant by the investigator
    - Events that meet PHL criteria but do not fulfil the above characteristics will be reported as a SAE with the investigator-reporter term (such as AST/ALT elevations, bilirubin elevation, transaminase elevation, etc.) per the investigator's discretion.
- Of note, all cases that meet the standard PHL criteria must be reported. The above characteristics are only to guide which reported term to use for these cases.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the Investigator will:
    - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
    - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
    - Complete Liver/PHL eCRF modules/forms as information becomes available.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria, to ensure timely analysis and SUSAR reporting to Health Authorities in an expedited manner. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** alternative explanation for the ALT or AST and TBL elevations:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to participants with liver metastases who meet PHL criteria on study treatment, having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on-study treatment occurrence of PHL criteria being met the Investigator will determine if there has been a **significant change** in the participants' condition[#] compared with the last visit where PHL criteria were met#

- If there is no significant change no action is required
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section E 4.2

E 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit (Section E 6).

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

> Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver disease?

If **No**: follow the process described in Section E 4.2 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant change in the participant's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section E 4.2 for reporting PHL as an SAE

E 8 Laboratory Tests

Proposed laboratory assessments to be performed as judged by the investigator	
Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNQ[a] IgG anti-HCV HCV RNA[b] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)[c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin[c] Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive
[c] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

E 9 References

Aithal et al, 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey M, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 89(6):806-15.

FDA Guidance for Industry, July 2009
FDA Guidance for Industry (July 2009) Drug-induced liver injury: premarketing clinical evaluation. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation. Accessed 06 April 2021.

Appendix F Cairo-Bishop Tumour Lysis Syndrome Definition and Grading Criteria (Howard Modification)

Laboratory tumour lysis syndrome (TLS) is defined as a level above or below normal, as defined below, for any 2 or more serum values of uric acid, potassium, phosphate, and calcium within 3 day before or 7 day after the initiation of anti-cancer therapy. This assessment assumes that a participant has or will receive adequate hydration and a hypouricemic agent(s).

Cairo-Bishop Definition of Laboratory Tumour Lysis Syndrome (Howard Modification)

Element	Value
Uric Acid	≥ 476 µmol/L (8 mg/dL)
Potassium	≥ 6.0 mmol/L (6 mg/L)
Inorganic phosphorus	≥ 1.45 mmol/L (4.5 mg/dL)
Calcium	≤ 1.75 mmol/L (7.0 mg/dL)

Howard et al 2011

Cairo-Bishop Definition of Clinical Tumour Lysis Syndrome

Clinical tumour lysis syndrome (TLS) assumes the laboratory evidence of metabolic changes and significant clinical toxicity that requires clinical intervention. Clinical TLS is defined as the presence of laboratory TLS and any 1 or more of the below-mentioned criteria. Maximal clinical TLS manifestation (renal, cardiac, neuro) defines the grade.

1 Creatinine ≥ 1.5 × ULN (age > 12 years or age adjusted)
2 Cardiac arrhythmia/sudden death
3 Seizure

Cairo-Bishop Clinical Tumour Lysis Syndrome Grading Criteria

	Grade					
Complication	**0**	**1**	**2**	**3**	**4**	**5**
Creatinine*,†	< 1.5 × ULN	1.5 × ULN	>1.5 – 3.0 × ULN	> 3.0 – 6.0 × ULN	> 6.0 × ULN	Death

Grade						
Complication	**0**	**1**	**2**	**3**	**4**	**5**
Cardiac Arrhythmia*	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with devise (eg, defibrillator)	Life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure*	None	None	One brief, generalised seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalised seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (eg, status epilepticus, intractable epilepsy)	Death

ADL = activities of daily living; CHF = congestive heart failure; CTLS = clinical tumour lysis syndrome; LTLS = laboratory tumour lysis syndrome; ULN = upper limit of normal
Clinical tumour lysis syndrome (CTLS) requires one or more clinical manifestations along with criteria for LTLS. Maximal CTLS manifestation (renal, cardiac, neuro) defines the grade.
*Not directly or probably attributable to therapeutic agent (eg, rise in creatinine after amphotericin administration).
†If no institutional ULN is specified, age/sex ULN creatinine may be defined as 105.6 µmol/L for female participants ≥ 16 years of age and 114.4 µmol/L for male participants ≥ 16 years of age.
Modified from Cairo and Bishop 2004.

Appendix G Strong Inhibitors and Inducers of CYP3A

Avoid co-administration of these agents with acalabrutinib, if possible. If not possible to avoid, monitor for toxicity (with inhibitors of CYP3A) and potential reduction in efficacy (with CYP3A inducers).

Strong Inhibitors of CYP3A[a]	Strong Inducers of CYP3A[e]
boceprevir	apalutamide
cobicistat[b]	carbamazepine[f]
clarithromycin[b]	enzalutamide
danoprevir and ritonavir[c]	mitotane
elvitegravir and ritonavir[c]	phenytoin[f]
grapefruit juice[d]	rifampin[f]
idelalisib	St John's wort[f]
indinavir and ritonavir[c]	
itraconazole[b]	
ketoconazole	
lopinavir and ritonavir[b,c]	
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[c]	
nefazodone	
nelfinavir	
posaconazole	
ritonavir[b,c]	
saquinavir and ritonavir[c]	
telaprevir	
tipranavir and ritonavir[c]	
telithromycin	
troleandomycin	
voriconazole	

[a] A strong inhibitor for CYP3A is defined as an inhibitor that increases the area under the concentration-time curve (AUC) of a substrate for CYP3A by ≥ 5-fold.

[b] In vivo inhibitor of P-glycoprotein.

[c] Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.

[d] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low-dose, single strength).

[e] A strong inducer for CYP3A is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate for CYP3A.

[f] In vivo inducer of P-glycoprotein.

Note: The list of drugs in this table is not exhaustive. Any questions about drugs not on this list should be addressed to the Medical Monitor of the protocol.

Source: FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo (Accessed 05 April 2020).

Appendix H Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the participant's safety. If in doubt, please contact the AZ Study Physician.

H 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections H 2 to H 6. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

H 2 Rescreening of Participants To Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The Investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in the schedule of assessments for the relevant module, the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participants in addition to that detailed in Section 5.4**.** The procedures detailed in the

schedule of assessments for the relevant module must be undertaken to confirm eligibility using the same randomisation number as for the participant.

H 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified health care professional (HCP) from the study site or third-party verification (TPV) service will visit the participant's home / or other remote location as per local standard operating procedures (SOPs), as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the clinical study protocol (CSP).

H 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow adverse events and concomitant medication to be reported and documented.

H 5 At-home or Remote Location IP Administration Instructions

If a site visit is not possible, at-home or remote location administration of IP may be performed by a qualified HCP, provided this is acceptable within local regulation/guidance. The option of at-home or remote location IP administration ensures participants safety in cases of a pandemic where participants may be at increased risk by traveling to the site/clinic. This will also minimise interruption of IP administration during other study disruptions, eg, site closures due to natural disaster.

H 5.1 At-home or Remote Location IP Administration by the Participant or His/Her Caregiver

Prior to at-home or remote location IP administration the Investigator must assess the participant or his/her caregiver to determine whether they are appropriate for at-home or remote location administration of IP. Once the participant or his/her caregiver is deemed appropriate for at-home or remote location administration, he/she must receive appropriate training. All necessary supplies and instructions for administration and documentation of IP administration will be provided. More information related to the visit can be obtained via a telemedicine or home / remote visit.

H 6 Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home / remote visits will be captured by the qualified HCP from the study site or TPV service.

Appendix I References

Armitage et al 2004
Armitage JO, Vose JM, Weisenburger DD. Towards understanding the peripheral T-cell lymphomas. Ann Oncol. 2004;15(10):1447-9.

Bellei et al 2017
Bellei M, Sabattini E, Pesce EA, Ko YH, Kim WS, Cabrera ME, et al. Pitfalls and major issues in the histologic diagnosis of peripheral T-cell lymphomas: results of the central review of 573 cases from the T-cell Project, an international, cooperative study. Hematol Oncol. 2017;35(4):630-6.

Boiko et al 2020
Boiko S, Proia TA, San Martin M, Gregory G, Wu MM, Aryal NK et al. Targeting Bfl-1 via acute CDK9 inhibition overcomes intrinsic BH3 mimetic resistance in lymphomas. Blood. 2021;137(21);2947-57.

Bray et al 2018
Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

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

Cancer Stat Facts: Hodgkin Lymphoma.
Cancer Stat Facts: Hodgkin Lymphoma. SEER NCI. Available at: https://seer.cancer.gov/statfacts/html/hodg.html. Accessed on 05 May 2021.

Cancer Stat Facts: Non-Hodgkin Lymphoma
Cancer Stat Facts: Non-Hodgkin Lymphoma. SEER NCI. Available at: https://seer.cancer.gov/statfacts/html/nhl.html. Accessed on: 05 May 2021.

Chen et al 2016
Chen R, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2016;128(12):1562-6.

Chen et al 2019
Chen R, Zinzani PL, Lee HJ, Armand P, Johnson NA, Brice P, Radford J, et al. Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087. Blood. 2019;134(14):1144-53.

Chen et al 2017
Chen R, Zinzani PL, Fanale MA, Armand P, Johnson NA, Brice P, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol. 2017;35(19):2125-32.

Cheson et al 2014
Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-68.

Cidado et al 2020
Cidado J, Boiko S, Proia T, Ferguson D, Criscione SW, San Martin M, et al. AZD4573 is a highly selective CDK9 inhibitor that suppresses MCL-1 and induces apoptosis in hematologic cancer cells. Clin Cancer Res. 2020;26(4):922-34.

Coiffier et al 2014
Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses. J Hematol Oncol. 2014;7:11.

Coiffier et al 2012
Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol. 2012;30(6):631-6.

Coiffier et al 2008
Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26(16):2767-78.

Connors et al 2020
Connors JM, Cozen W, Steidl C, Carbone A, Hoppe RT, Flechtner HH, et al. Hodgkin lymphoma. Nat Rev Dis Primers. 2020;6(1):61.

Correa and O'Conor 1971
Correa P, O'Conor GT. Epidemiologic patterns of Hodgkin's disease. Int J Cancer. 1971;8(2):192-201.

de Charette and Houot 2018
de Charette M, Houot R. Hide or defend, the two strategies of lymphoma immune evasion: potential implications for immunotherapy. Haematologica. 2018;103(8):1256-68.

EMA-CTFG-EC 2021
European Medicines Agency (EMA), Clinical Trials Facilitation and Coordination Group (CTFG), European Commission (EC). Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic, Version 4, 04 February 2021.

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. Accessed on 14 May 2021.

FDA 2020
US Food and Drug Administration (FDA). FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency, March 2020 (updated 27 January 2021). https://www.fda.gov/media/136238/download. Accessed on 14 May 2021.

Fiore et al 2020
Fiore D, Cappelli LV, Broccoli A, Zinzani PL, Chan WC, Inghirami G. Peripheral T-cell lymphomas: from the bench to the clinic. Nat Rev Cancer. 2020;20(6):323-42.

Glaser and Jarrett 1996
Glaser SL, Jarrett RF. The epidemiology of Hodgkin's disease. Baillieres Clin Haematol. 1996;9(3):401-16.

GLOBOCAN 2020
Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. https://gco.iarc.fr/today. Accessed 08 June 2021.

Gopal et al 2015
Gopal AK, Chen R, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Blood. 2015;125(8):1236-43.

Howard et al 2016
Howard SC, Trifilio S, Gregory TK, Baxter N, McBride A. Tumor lysis syndrome in the era of novel and targeted agents in patients with hematologic malignancies: a systematic review. Ann Hematol. 2016;95(4):563-73.

Howard et al 2011
Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-54. Erratum in: N Engl J Med. 2018;379(11):1094.

Iwanaga 2020
Iwanaga M. Epidemiology of HTLV-1 Infection and ATL in Japan: an update. Front Microbiol. 2020;11:1124.

Jones et al 2015
Jones GL, Will A, Jackson GH, Webb NJ, Rule S. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. Br J Haematol. 2015;169(5):661-71.

Kumar et al 2019
Kumar A, Sha F, Toure A, Dogan A, Ni A, Batlevi CL, et al. Patterns of survival in patients with recurrent mantle cell lymphoma in the modern era: progressive shortening in response duration and survival after each relapse. Blood Cancer J. 2019;9(6):50.

Kuruvilla et al 2021
Kuruvilla J, Ramchandren R, Santoro A, Paszkiewicz-Kozik E, Gasiorowski R, Johnson NA, et al. Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study. Lancet Oncol. 2021;22(4):512-524. Erratum in: Lancet Oncol. 2021;22(5):e184.

Mak et al 2013
Mak V, Hamm J, Chhanabhai M, Shenkier T, Klasa R, Sehn LH, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. J Clin Oncol. 2013;31(16):1970-6.

Nakatsuka and Aozasa 2006
Nakatsuka S, Aozasa K. Epidemiology and pathologic features of Hodgkin lymphoma. Int J Hematol. 2006;83(5):391-7.

O'Connor et al 2015
O'Connor OA, Horwitz S, Masszi T, Van Hoof A, Brown P, Doorduijn J, et al. Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: results of the pivotal phase II BELIEF (CLN-19) study. J Clin Oncol. 2015;33(23):2492-9.

O'Connor et al 2011
O'Connor OA, Pro B, Pinter-Brown L, Bartlett N, Popplewell L, Coiffier B, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol. 2011;29(9):1182-9.

Park and Ko 2014
Park S, Ko YH. Peripheral T-cell lymphoma in Asia. Int J Hematol. 2014;99(3):227-39.

Pro et al 2012
Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. J Clin Oncol. 2012;30(18):2190-6.

Strachan and Read 1991
Strachan T, Read AP. Human Molecular Genetics 2. New York: Wiley-Liss; 1999.

Swedlow et al 2017
Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. WHO Classification of Tumours, Revised 4th Edition, Volume 2. IARC, 2017.

Vassilakopoulos et al 2020
Vassilakopoulos TP, Asimakopoulos JV, Konstantopoulos K, Angelopoulou MK. Optimizing outcomes in relapsed/refractory Hodgkin lymphoma: a review of current and forthcoming therapeutic strategies. Ther Adv Hematol. 2020;11:2040620720902911.

Xia et al 2020
Xia Y, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for patients with cancer. Lancet Oncol. 2020;21(4):e180.

Yu et al 2020
Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 Transmission in Patients with Cancer at a Tertiary Care Hospital in Wuhan, China. JAMA Oncol. 2020;6(7):1108-10.

Zain 2019
Zain JM. Aggressive T-cell lymphomas: 2019 updates on diagnosis, risk stratification, and management. Am J Hematol. 2019;94(8):929-46.

Zhang et al 2020
Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. Ann Oncol. 2020; 31(7):894-901.

Appendix J Abbreviations

Abbreviation or special term	Explanation
ABC	Activated B-cell
AE	Adverse event
AESI	Adverse event of special interest
ALC	Absolute lymphocyte count
ALL	Acute lymphocytic leukaemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
Anti-HBc	Hepatitis B core antibody
aPTT	Partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BCL2	B-cell Lymphoma-2
BCL-XL	B-cell lymphoma extra large
BCR	B-cell receptor
BR	Bendamustine and rituximab
BTK	Bruton's tyrosine kinase
CBC	Complete blood count
CD	Carbohydrate deficient
CDK9	Cyclin-dependent kinase 9
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLL	Chronic lymphocytic leukaemia
Cmax	Maximum concentration
CMML	Chronic myelomonocytic leukaemia
CMV	Cytomegalovirus

Abbreviation or special term	Explanation
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatinine phosphokinase
CR	Complete response / Complete remission
CRO	Contract research organisation
CRR	Complete response rate
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Carboxyl-terminal domain
CTFG	Clinical Trials Facilitation and Coordination Group
CYP	Cytochrome P450
DILI	Drug-Induced Liver Injury
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DoR	Duration of response
DSIF	5,6-dichloro-1-β-D-ribofuranosylbenzimidazole sensitivity inducing factor
DSUR	Development Safety Update Report
DU	Dose is unsafe
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Case Report Form (electronic/paper)
EDC	Electronic data capture
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose

Abbreviation or special term	Explanation
FFPE	Formalin-fixed paraffin embedded
FTIH	First-time-in-human
GCB	Germinal centre B-cell
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony-stimulating factor
GGT	Gamma-glutamyl transferase
GLDH	Glutamic dehydrogenase
GLP	Good Laboratory Practice
gmean	Geometric mean
HBV	Hepatitis B virus
HCP	Health care professional
HCV	Hepatitis C virus
hERG	Human Ether-à-go-go-Related Gene
HGBCL	High-grade B-cell lymphoma
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HL	Hy's Law
HR	Hazard ratio
IATA	International Airline Transportation
IC50	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Committee on Harmonisation
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
INR	International Normalised Ratio
IP	Investigational product
IR	Idelalisib and rituximab
IRB	Institutional Review Board
IRC	Independent Review Committee
IV	Intravenous

Abbreviation or special term	Explanation
IVRS	Interactive Voice Response Systems
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LCT	Liver chemistry test
LRTI	Lower respiratory tract infection
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
MALT	Mucosa-associated lymphoid tissue
MATE	Multi-antimicrobial extrusion
MCL	Myeloid Cell Leukaemia
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
CCI	CCI
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTPI-2	modified toxicity probability interval
MUGA	Multigated acquisition scan
MYC	Myelocytomatosis
MZL	Marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NELF	Negative elongation factor
NHL	Non-Hodgkin lymphoma
NK	Natural killer
OAE	Other significant adverse event
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
ORR	Objective response rate

Abbreviation or special term	Explanation
OS	Overall survival
CCI [redacted]	CCI [redacted]
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron-emission tomography
PFS	Progression-free survival
PHL	Potential Hy's Law
PK	Pharmacokinetics
PKPD	Pharmacokinetic-pharmacodynamic
PMBCL	Primary mediastinal B-cell lymphoma
PML	Progressive Multifocal Leukoencephalopathy
PR	Partial response / Partial remission
PT	Prothrombin time
P-TEFb	Positive transcription elongation factor b
pSer2RNAP2	Phosphorylation levels of Serine 2(Ser2) found in the carboxyl-terminus (CTD) of RNA polymerase II (RNAP2)
QT	ECG interval measured from the onset of the QRS complex to the end of the T-wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected using Fridericia's formula (QTcF)
RCHOP	Rituximab and chemotherapy combination therapy
RNAP2	RNA polymerase II
r/r	Relapsed/refractory
RP2D	Recommended Phase II dose
SAE	Serious adverse event (see definition in Appendix B)
SAP	Statistical Analysis Plan
SCT	Stem cell transplantation
SD	Stable disease
Ser2	Serine 2
SFU	Safety follow-up

Abbreviation or special term	Explanation
SLL	Small lymphocytic lymphoma
SoA	Schedule of Activities
SoC	Standard of care
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TLS	Tumour lysis syndrome
TPV	Third-party verification
TSH	Thyroid-stimulating hormone
TTNT	Time to next treatment
TTR	Time to response
ULN	Upper limit of normal

Appendix K Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1 [03 July 2020]

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

Overall Rationale for the Amendment:

This protocol amendment incorporates changes requested by the FDA arising from review of version 1 of the protocol.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Core protocol			
5.1 Inclusion Criteria - Core	Removal of serum creatinine from Table 2 (Criteria for Adequate Organ Function); update of calculated creatinine clearance from ≥ 50 mL/minute to ≥ 60 mL/minute; inclusion criterion 8 amended to specify that participants should be able to swallow capsules intact without difficulty.	Amended in response to FDA request.	Substantial
Module 1			
13.1 Overall design	Statement added to clarify that no further intra-patient dose escalation (other than the ramp up to the assigned target dose level) will be allowed.	Clarification as per FDA request.	Non-substantial
13.3 Justification for Dose	Information regarding TLS events and DLTs from Study D8230C00001 (Phase I AZD4573 monotherapy) updated in line with most recent information from ongoing FTIH study.	Updated in line with response to FDA request.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Confirmation added that the planned starting dose regimen for the AZD4573/acalabrutinib combination is 9 mg AZD4573 once weekly, following SRC declaration that AZD4573 12 mg once weekly is a tolerated dose.	Updated in line with response to FDA request.	Substantial
14.1 Inclusion Criteria	Wording for inclusion criterion 2 clarified. Inclusion criterion 4 amended to state participants must have failed at least 2 prior therapies instead of 1.	Amended in response to FDA request.	Substantial
14.2 Exclusion Criteria	Addition of 2 exclusion criteria regarding participants on anticoagulant therapy due to risk of bleeding as a potential overlapping toxicity with AZD4573 and acalabrutinib.	Updated in line with response to FDA request.	Substantial
15.2 Starting Dose, Dose-Escalation Scheme, and Stopping Criteria	Amended to add additional safety monitoring after the DLT-assessment period and potential stopping criteria.	Amended in response to FDA request.	Substantial
15.3 Definition of Dose-limiting Toxicity (DLT)	DLT criteria timing updated to include within 72 hours of onset of toxicity, for consistency with the threshold for duration of non-haematologic toxicities ≥ Grade 3.	Updated in line with response to FDA request.	Substantial
	DLT criteria for febrile neutropenia and thrombocytopenia updated.	Updated in line with response to FDA request.	Substantial
	Definition of isolated changes in GGT in DLT criteria exclusions updated to clarify that this exception only applies to genuinely isolated elevations of GGT. Exclusions pertaining to TLS removed.	Amended in response to FDA request.	Substantial
15.11.2 Prohibited Concomitant Therapy	Inclusion of warfarin or equivalent vitamin K antagonists	Amended in response to FDA request.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	as a prohibited therapy due to risk of bleeding as a potential overlapping toxicity with AZD4573 and acalabrutinib.		
17.1.9.6 Haemorrhage	Addition of requirement that acalabrutinib treatment must be discontinued if participants require either a vitamin K antagonist or combined administration of antiplatelet and therapeutic anticoagulation while on study, due to risk of bleeding as a potential overlapping toxicity with AZD4573 and acalabrutinib.	Amended in response to FDA request.	Substantial
18.6 Safety Review Committee	Amended to add additional safety monitoring and potential stopping criteria.	Amended in response to FDA request.	Substantial

Amendment 2 21 Jul 2021

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

Overall Rationale for the Amendment

This protocol amendment expands the disease population in Module 1 to include participants with r/r MZL, and adds the new Module 2.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
1.1 Synopsis, 6 Study Intervention - Core	Synopsis updated to reflect the amended text in the body text for Core and Module 1, and the addition of Module 2 Recruitment of participants with r/r MZL added to Module 1	Expansion of disease population in Module 1	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
1.1 Synopsis, **Module 2 (United States) – NEW,** Sections 19 through 27	Module 2 – Part A: AZD4573 monotherapy window followed by combination therapy with acalabrutinib. Part B study design to be determined from emerging Part A data	Additional Module	Substantial
2.2.6 Clinical Experience with AZD4573	Study data for ongoing FTIH study updated, including data in Table 1	To align with updated IB and emerging data from ongoing FTIH study	Non-substantial
2.3.1 Risk Assessment, 4.1 Overall Design, 8.2.10 Reporting of SAEs, 10.2 SoAs – Module 1	Requirement for overnight hospitalisation amended	Based on emerging data from ongoing FTIH study	Substantial
3 Objectives and Endpoints, 10.2 SoAs – Module 1, 12 Objectives and Endpoints – Module 1, 17 Study Assessments and Procedures – Module 1, and 17.9 Exploratory Whole Blood Analysis Samples – NEW, 17.10.4.1 CCI Sample for CCI Isolation	Exploratory CCI sample collection added, including CCI sample CCI exploratory objectives/endpoints for CCI updated	CCI	Substantial
3 Objectives and Endpoints, 5.1 Inclusion Criteria - Core, 10.2, SoAs – Module 1 17.11 Optional Genomics Initiative Sample, and Appendix D 2 Genetic Research Plan and Procedures	Genomic initiative tissue source changed from blood to saliva	A saliva sample is more appropriate for this participant population	Non-substantial
3 Objectives and Endpoints and 4.1 Overall Design	Allowance for dose confirmation instead of dose setting added	For some new disease populations, dose confirmation is needed rather than dose setting	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
4.1 Overall Design, 6 Study Intervention - Core, 10.1 Schema, 11.2 Acalabrutinib Background, 11.3.1 Risk Assessment, 13.1 Overall Design, 13.2.2 MZL Participants - NEW, and 14.1 Inclusion Criteria	Module 1 description amended to include r/r MZL participants	To recruit a more inclusive and diverse real-world participant population while maintaining safeguards for participant safety	Substantial
4.1 Overall Design	Clarification that the SRC will review PK data *when available*	PK data may not always be available at the time of SRC meetings	Non-substantial
2.2.6 Clinical Experience With AZD4573	Study data for ongoing FTIH study updated	Emerging data from ongoing FTIH study	Non-substantial
5.1 Inclusion Criteria – Core	Inclusion criterion #5: lipase and amylase criteria were updated	The potential risk of pancreatic injury is based on preclinical data only. There are no emergent significant clinical data to support the risk of pancreatic injury, therefore the thresholds for lipase and amylase values were revised to be more inclusive	Non-substantial
6.1.1 Investigational Products, 17.1.6 Clinical Safety Laboratory Assessments, and 17.1.10.9 Liver Chemistry Test Abnormalities and the Risk of Liver Injury	LCT requirements for participants with elevated transaminases updated	Liver chemistry values (AST, ALT, bilirubin) were updated to be aligned with the latest international guidance by DILI experts	Non-substantial
6.11 Prior/Concomitant Therapy, 15.11.3 AZD4573 and Concomitant Therapy, and Appendix A 11 Study Protocol Requirements During the 2019-Novel Corona Virus Outbreak (COVID-19)	Recommendation regarding administration of non-live inactivated vaccines added	To avoid biases in safety data due to potential vaccine-related AEs	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
6.12 Dose Modification	Dose modification clarified that for AEs possibly related to AZD4573, study drug may be temporarily or permanently stopped, or reduced	Clarification of dose modification options	Non-substantial
8.2.1 Time Period and Frequency for Collecting AE and SAE Information	Aligned timing for AE collection with timing for SAEs	To correct for AE collection starting at informed consent	Non-substantial
8.2.8 New Cancers - NEW	New Cancers section added	Company instructions for safety reporting	Non-substantial
8.2.9 Handling of Deaths - NEW	Handling of Deaths section added	Company instructions for safety reporting	Non-substantial
13.1 Overall Design	Data cut-off for the primary analysis for each expansion subgroup changed from after all participants have had the opportunity to be followed for at least 12 months to at least 6 months	Based on providing sufficient opportunity to respond to study treatment for the primary endpoint of ORR, and on expected PFS in the current target population, data cut-off for primary analysis after all participants have had the opportunity to be followed for at least 6 months is considered to best serve the objectives of the study	Substantial
11.1 Study Rationale – Module 1, 13.1 Overall Design, 14.1 Inclusion Criteria, 17.10.1 Collection of Archival Tumour Samples, 23.1 Inclusion Criteria, and 26.10.1 Collection of Archival Tumour Samples	Made clear that participants will be enrolled based on pathology report	Actual tumour samples will not be available at Screening	Non-substantial
17.1.1 Enrolment and Screening	Tobacco use will no longer be collected	New corporate policy	Non-substantial
17.2.1 Adverse Events of Special Interest for Acalabrutinib - NEW	AESIs for acalabrutinib added	To align with updated acalabrutinib IB v 10	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
17.4.2	The disease assessment schedule for CT and PET updated to include mandatory scheduled PET scans post-baseline	Per the requirements of Lugano 2014 Response Criteria	Substantial
Appendix E 4.2 Potential Hy's Law Criteria Met, Appendix E 5 Review and Assessment of Potential Hy's Law Cases, Appendix E 8 Laboratory Tests Appendix E 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment - NEW	Information regarding Hy's Law updated	Clarification	Non-substantial
Appendix H Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis - NEW	Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis section added	Due to COVID-19 pandemic	Non-substantial
Appendix J - NEW	Protocol amendment history section added	Previous amendment summary moved from cover pages, per template	Non-substantial
General	Possible reporting of exploratory analyses in the CSR removed throughout the document	No plans for exploratory analyses prior to submission of the CSR	Non-substantial
	TLS monitoring will use the Howard modification of Cairo-Bishop criteria – change made throughout the document	Refined version of the criteria	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
1.1, 2.1, 2.2.4, 2.3.1, 3, 4.3.2, 5.1, 5.2, 5.3.1, 6.2, 6.9, 6.11, 8.2.2, 8.2.5, 8.2.6, 8.2.10, 8.2.12, 8.3, 10.2, 11.1, 11.2.1, 11.3, 14, 14.3.1 – NEW, 15.2, 15.3, 15.10, 15.11.1, 15.11.2, 15.12.1, 17.1, 17.4.3, 17.4.4, 17.6, 17.7, 17.8, 17.10, 18.2, 18.3, 18.4.4, 18.4.5, 18.6, 28, Appendix A 9, Appendix A 11, Appendix B 2, Appendix F, and Appendix I	Updates or new information added throughout the document for consistency across sections, updates for clarity, and edits made based on completeness of information which are not considered significant	Minor, therefore have not been summarised	Non-substantial
	Minor editorial and document formatting revisions	Minor, therefore have not been summarised	Non-substantial

Amendment 3, 01 August 2022

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

Overall Rationale for the Amendment

This protocol amendment changes to allow up to approximately 21 patients (dose-limiting toxicity evaluable) per dose level in the backfill of Module 1 part A to make the study more available for the all-comer diffuse large B-cell lymphoma population and reduces the amount of assessments from Cycle 9 onwards. Furthermore, updates are made to secure consistency within the protocol, correct errors, and provide clarifications.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
Schedule of Activities-Module 1 Table 4 Part A-Dose setting Cohorts Table 5 Part B-Expansion Schedule of Activities-Module 2 Table 23 Part A, Period 1 Table 24 Part A, Period 2 And body text throughout the document	Updates added throughout the SoA tables and footnotes to reflect the instructions given in the in-text Sections of the protocol, for consistency with the instructions given in the footnotes, to clarify ambiguous wording, to clarify definitions, and to correct typing errors.	Clarification and consistency	Non-substantial
Section 1.1 Synopsis Section 13.1 Overall Design (Module 1)	Module 1 Part A, clarified to allow up to approximately 21 patients to be included.	Clarification	Non-substantial
Section 4.1 Overall Design (Core) Section 15.2 Starting Dose, Dose-Escalation Scheme, and Stopping Criteria	Literature reference to Goy et al removed	Correction of an error	Non-substantial
Section 5.2 Exclusion Criteria-Core	Reduced the CAR-T exclusion criterion to within 60 days prior to first dose of study drug	To make the study available to more patients, increasing the population of R/R DLBCL patients who progressed after prior CAR-T treatment	Substantial
Section 5.2 Exclusion Criteria-Core	Removed neutropenia from Exclusion Criterion 2, as this was an error	Correction of error	Non-Substantial
Section 8.2.2 Follow-up of AEs and SAEs	Added that “Detailed information on the event (symptoms and signs, work-up done)” will be collected following SAE	Clarification	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
Section 1.1 Synopsis Section 13.1 Overall Design (Module 1) Section 18.2 Sample Size Determination Figure 4 Module 1 Overall Study Design	Module 1 part B, changed so that any safe dose level can be backfilled up to approximately 21 patients instead of 12.	To make study available to all-comer DLBCL population	Substantial
Section13.1, Table 8 Dosing Schedule- Module 1	Clarified the DLT-assessment period in footnote	Clarification	Non-substantial
Section 14.1 Inclusion Criteria (Module 1)	Included instructions for how to handle participants who do not have a viable biopsy.	To make the study available to more patients who accept to undergo all biopsy assessments required per protocol	Non-substantial
Section 14.2 Exclusion Criteria (Module 1)	Removed exclusion criterion for BTK inhibitors.	Prior BTK inhibitor treatments do not preclude potential efficacy of the AZD4573 + acalabrutinib combination. Hence, such patients shall not be excluded from the study.	Substantial
Section 14.2 Exclusion Criteria (Module 1) Section 1.1 Synopsis	Clarified the use of anticoagulants	Clarification	Non-substantial
Dose Modification Section 15.12 Section 24.9	Clarified wording for maximal drug interruption for *related* toxicity	Clarification	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
Schedule of Activities-Module 1 Table 4 Table 5 Schedule of Activities-Module 2 Table 23 Table 24 Study Assessments and Procedures (Module 1) Section 17.1 Enrolment and Screening Study Assessments and Procedures (Module 2) Section 26.1 Safety Assessments	Change to have less frequent assessments starting Cycle 9 instead of Cycle 13	To reduce burden for the patient	Substantial
Section 17.4.1 and Section 26.4.1 Lugano Modification of Ann Arbor Staging System Table 17 Table 35	Reinstated Ann Arbor staging system tables to this protocol version	Tables were previously in Protocol Amendment 1; they were unintentionally deleted when Amendment 2 was published. Reinstated in this protocol version.	Non-substantial
Lugano Response Criteria for NHL Table 18 Table 36	Added footnote to define Deauville score for complete metabolic response	Clarification	Non-substantial
Table 4 Table 5 Table 23 Table 24 And body text throughout the document	Timing of Lipase/Amylase, urine samples, cardiac troponin and T4/cortisol/ACTH/TSH samples aligned with haematology and chemistry samples	Simplification, alignment of timepoints, less impact on patient	Non-substantial
Section 17.7.1 Collection of Samples (Part A and Part B) Section 26.7.1 Collection of Samples	Pharmacodynamic samples will be whole blood, CCI [redacted]	Correction of an error	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
Mandatory TLS Prophylaxis Guidance Table 16 Table 34	Changed dose of allopurinol to once daily	Correction, based on local standard of care many investigators consider 300 mg twice daily to be too high dose	Non-substantial
Survival Follow-up Section 17.1.9.3 Section 26.1.9.3	Added clarification of how the survival follow-up should be performed.	Clarification	Non-substantial
Section 17.4.2, Table 19	Footnote that was included in error removed	Correction of an error	Non-substantial
Section 19 and throughout the document	Removed mention that Module 2 part of the study is for US only.	To make the study available for patients in selected countries	Non-substantial
Section 26.6 Pharmacokinetics	Part A, Periods 1 and 2 were split into separate descriptions	Clarification	Non-substantial
Section 26.8 Exploratory [redacted] Samples (Module 2) Table 24 Schedule of Activities-Module 2, Part A, Period 2	Removed [redacted] in Module 2 Part 2	Simplification	Non-substantial
Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law	Updated PHL process	Adapt the PHL reporting process to reflect the current experience of the AZD4573 liver safety profile.	Substantial
Appendix E 8, Laboratory Tests	Updated title in the table in E8 laboratory tests	This Section was for a central lab receiving chemistry tests and is not applicable to this study	Non-substantial

Abbreviations: ACTH = adrenocorticotropic hormone; BTK = Bruton's tyrosine kinase; CDK9 = cyclin-dependent kinase 9; DLBCL = diffuse large B-cell lymphoma; DLT = dose-limiting toxicity; NHL = non-Hodgkin lymphoma; PHL = potential Hy's law; PMBC = Peripheral blood mononuclear cell; SAE = serious adverse event; T4 = thyroxine;TSH = thyroid-stimulating hormone.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d8230c00002-csp-v5		
Document Title:	D8230C00002 Clinical Study Protocol version 5	
Document ID:	Doc ID-004236033	
Version Label:	5.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
06-Jun-2023 03:37 UTC	PPD	Content Approval
05-Jun-2023 11:25 UTC	PPD	Author Approval
05-Jun-2023 20:44 UTC	PPD	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.