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

ClinicalTrials.gov Identifier: **NCT05140382**

Clinical Study Protocol: version 2.0, dated 09 Sep 2021

Clinical Study Protocol	
Study Intervention	AZD4573
Study Code	D8231C00001
Version	2.0
Date	09 Sep 2021

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

Sponsor Name: AstraZeneca

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Regulatory Agency Identifier Numbers

EudraCT number: 2021-002570-54

IND number: 156169

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

Protocol Number: D8231C00001

Amendment Number: 1
Study Intervention: AZD4573
Study Phase: Phase II

Short Title: AZD4573 as Monotherapy or in Combination with Anti-cancer Agents in Patients with r/r PTCL or r/r cHL

Study Physician Name and Contact Information will be provided separately

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Version 2.0, Amendment 1	09-Sep-2021
Version 1.0	25-Jun-2021

The Protocol Amendment Summary of Changes table is provided below for the current amendment.

Version 2.0, Amendment 1 (09 September 2021)

Overall Rationale for the Amendment:

This protocol amendment incorporates changes requested by the FDA arising from review of version 1.0 of the protocol.

The Clinical Study Protocol (CSP), Version 1.0, dated 25 June 2021, was updated with the following changes:

Section # and Name	Description of Change	Brief Rationale
Title page	Regulatory Agency Identifier Numbers updated.	Correction of typographical error in EudraCT number. IND number added.
Section 1.1 Synopsis	Text related to objective response rate removed from primary and secondary efficacy objectives in the Core Objectives table to align with Table 3, Section 3 (Objectives and Endpoints), and Section 10.9.4.2.2 (Secondary Efficacy Endpoints) and due to a typographical error in secondary	Typographical error in secondary objectives ("by evaluation of objective response rate").

Section # and Name	Description of Change	Brief Rationale
	objectives (objective response rate not evaluated).	
Section 5.1 Inclusion Criteria	Inclusion criteria in Module 1 (Section 10.5.1) have been moved to the Core protocol (Section 5.1).	Updated in line with response to FDA request.
Section 5.2 Exclusion Criteria	Exclusion criteria from Module 1 (Section 10.5.2) have been moved to the Core protocol (Section 5.2).	Updated in line with response to FDA request.
Section 7.1 Discontinuation of Study Intervention	Text moved to new section 7.1.1. dedicated to study-wide stopping rules for safety.	Amended in line with response to FDA request.
Section 7.1.1 Criteria for stopping or pausing the study recruitment	New section added to specify in greater detail study-wide stopping rules for safety that would trigger SRC evaluation and potential study pause.	New text added in line with response to FDA request.
Section 10.1.2 Schedule of Activities, footnote c; Section 10.8.2.5 Clinical Safety Laboratory Assessments	Footnote was updated and Section 10.8.2.5 amended for clarification of the haematologic and chemistry criteria required to initiate each cycle of therapy.	Clarification as per FDA request.
Section 10.4.1 Module 1 Design: AZD4573 monotherapy	Inclusion of a requirement for pooled safety monitoring assessments to be conducted at 3-monthly intervals.	Amended in line with response to FDA request.
Section 10.5.1 Additional Module 1 Inclusion Criteria	All additional module 1 inclusion criteria were moved to Section 5.1 Inclusion Criteria.	Updated in line with response to FDA request.
Section 10.5.2 Additional Module 1 Exclusion Criteria	All additional module 1 exclusion criteria were moved to Section 5.2 Exclusion Criteria.	Updated in line with response to FDA request.

Section # and Name	Description of Change	Brief Rationale
Section 10.6.1 Dose Modification	Update of Grade 3 or 4 non-haematological toxicities Table 11 to add the guidance of one dose level reduction in order to resume AZD4573 dosing after resolution of a Grade 4 non-haematological (excluding liver and TLS) AE to Grade 1, and guidance on discontinuation following a third occurrence.	Amended in line with response to FDA request.

In addition, minor formatting and editorial changes were made throughout the CSP.

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1 PROTOCOL SUMMARY

1.1 Synopsis

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

Short Title: AZD4573 as Monotherapy or in Combination with Anti-cancer Agents in Patients with r/r PTCL or r/r cHL

Rationale: The study is designed to establish the efficacy of AZD4573, administered as monotherapy or combination therapy, to participants with either relapsed/refractory (r/r) peripheral T-cell lymphoma (PTCL) or r/r classical Hodgkin Lymphoma (cHL). The study will also confirm the safety profile and pharmacokinetics (PK) of the module-defined AZD4573 monotherapy or combination therapy in these populations.

Core Objectives

	Type	Objectives
Primary	Efficacy	To assess the efficacy of the module-defined study treatment in participants with either r/r PTCL or r/r cHL by evaluation of module-defined endpoints.
Secondary	Efficacy	To assess the efficacy of the module-defined study treatment in participants with either r/r PTCL or r/r cHL by evaluation of module-defined endpoints.
	Safety	To assess the safety and tolerability of the module-defined study treatment.
	PK	To assess the plasma/serum PK of AZD4573 and/or other module defined anti-cancer agents when given in combination (as applicable).

Abbreviations: cHL classical Hodgkin Lymphoma; PK, pharmacokinetics; PTCL, peripheral T-cell lymphoma; r/r, relapsed/refractory.

For endpoints and exploratory objectives, see Section 3 of the protocol. For module-specific endpoints, see the relevant module.

Overall Design: This is a modular, Phase II, multicentre, open-label, dose confirmation and expansion study in participants with relapsed/refractory PTCL or cHL. The modular design of this study allows evaluation of AZD4573 as monotherapy or in combination with other anti-cancer agents. The core study design is to assess the efficacy of AZD4573, administered as monotherapy or combination therapy, to participants with either r/r PTCL or r/r cHL and to confirm the safety profiles and PK in these populations. This study will use the established RP2D of AZD4573 for lymphoma (12 mg weekly, starting with an intra-participant dose ramp-up), as assessed in the ongoing Phase I monotherapy study of AZD4573 (D8230C00001). This dose will not be exceeded during the study. Further modules may be added via protocol amendment. Study information applicable to all participants in this study is described in the core sections of this protocol; the rationale for each study treatment and cohort, and specific study information and assessments, will be described in each separate module. This study is planned to take place in approximately 30 centres across 10 countries. Module 1 will assess the efficacy, safety, tolerability and PK of AZD4573 as a monotherapy in r/r PTCL and r/r cHL populations and explore pharmacodynamics in these disease subtypes. If one or more cohorts in Module 1 show a favourable safety and efficacy profile by the primary analysis then an AZD4573 monotherapy Phase II expansion may be added via a protocol amendment. Additional modules may also be added via substantial protocol amendments to assess AZD4573 in combination with other anti-cancer agents in r/r PTCL or r/r cHL based on emerging preclinical and clinical data and study rationale.

Disclosure Statement: This is a modular, multicentre, open-label, dose confirmation and expansion study with no masking.

Number of Participants: Module 1 only - in Module 1, a maximum of approximately 90 response-evaluable participants will be treated with study intervention across 3 disease cohorts.

Table 1 Module 1: Planned Response-evaluable Participant Population

Cohort	Population	Number of participants[a]	Line of therapy
Cohort 1	PTCL, all comers (excluding NKTCL)	21	2+
Cohort 2	PTCL (NKTCL only)	21	2+
Cohort 3	cHL	21	3+

[a] CCI [redacted]

Abbreviations: cHL classical Hodgkin Lymphoma; NKTCL, natural killer/T-cell lymphoma; PTCL, peripheral T-cell lymphoma

Intervention Groups and Duration: This protocol has a modular design, with the potential for future modules investigating AZD4573 in combination with other anticancer agents to be added via protocol amendment. Module 1 will consist of 2 r/r PTCL cohorts and 1 r/r cHL cohort. Each Module 1 cohort will include an intra-participant dose ramp-up (Cycle 1), during which participants will receive a single dose of AZD4573 once weekly beginning with 6 mg Week 1, 9 mg Week 2, and 12 mg for each of Weeks 3 to 5. The target dose following the ramp-up is 12 mg attained on Week 3 of Cycle 1. Every cycle beyond Cycle 1 will be 3 weeks in length and participants will receive 12 mg infusions of AZD4573 once weekly until progression. All participants will continue to be followed until death, lost to follow-up, sponsor closes the study, or withdrawal of consent, whichever occurs first.

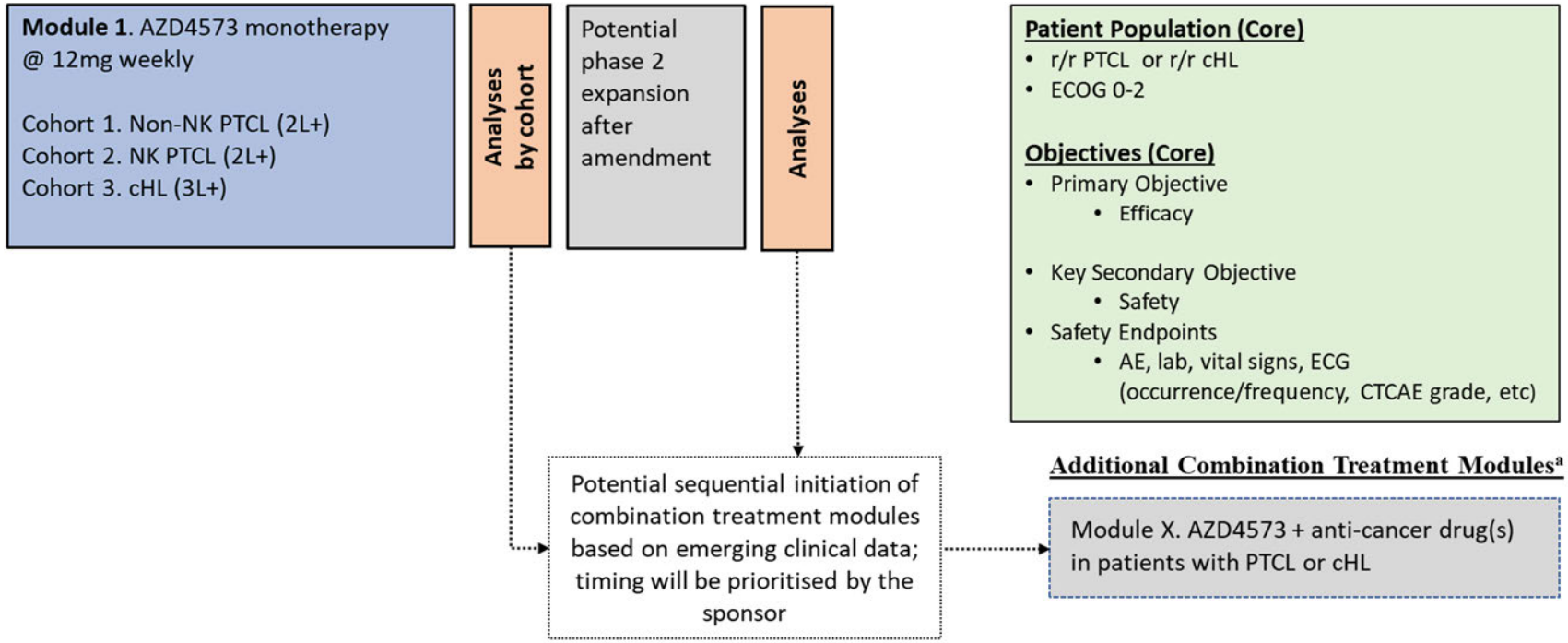
Data Monitoring Committee: There will be no formal data monitoring committee for this study. A study-specific Safety Review Committee (SRC) will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety, PK, and other relevant data (see study design section of the relevant module).

Statistical Methods: In Module 1, the data cut-off (DCO) for the primary analysis for each cohort will occur after all response-evaluable participants in the cohort have had the opportunity to be followed for at least 6 months since their first dose or have progressed or have initiated other anticancer therapy, or when 75% of participants have progressed or died, whichever occurs first. Additional data cuts may also be performed, if required. At the end of each module a final analysis will be conducted to incorporate all data (up to and beyond the primary analysis) from all participants in the module. For all modules, the primary efficacy endpoint is ORR. For Module 1, ORR is measured in terms of the Lugano criteria. Secondary efficacy endpoints for Module 1 include CR rate, DoR, PFS and OS. Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs and ECG data for all modules. AEs will be graded according to the NCI CTCAE Version 5.0. The number and percentage of participants with TEAEs in different categories (eg, causally related, CTCAE Grade $\geq$ 3, etc.) will be summarised by cohort; 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 occurs. Data will be presented by cohort. Descriptive statistics will be used for all variables. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated based on the population total by cohort and by timepoint as appropriate.

1.2 Schema

Please see the individual schema for each study module within the respective protocol section.

Figure 1 AZD4573 Modular Phase II CSP in r/r PTCL and r/r cHL



[a] Additional AZD4573 combination modules in r/r PTCL or r/r cHL may be added pending new pre-clinical/clinical data. Combination risk assessment for PTCL and cHL to be performed when their respective clinical monotherapy profiles are understood.

Abbreviations: AE, adverse events; cHL, classical Hodgkin Lymphoma; CSP, clinical study protocol; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; lab, clinical laboratory results; NK PTCL, natural killer/peripheral T-cell lymphoma; r/r, relapsed/refractory.

1.3 Schedule of Activities

Please see the individual SoA for each study module within the respective protocol section.

2 INTRODUCTION

AZD4573 is a potent, selective inhibitor of CDK9 that is being developed as a monotherapy and/or combination therapy for the treatment of several haematological malignancies, including r/r PTCL and r/r cHL.

2.1 Study Rationale

This is a modular, Phase II, multicentre, open label study of AZD4573 administered intravenously as monotherapy or in combination with other anti-cancer agents, to participants with r/r PTCL or r/r cHL.

As a CDK9 inhibitor, treatment with AZD4573 leads to rapid depletion of short lived gene transcripts, including *MCL1* and *BFL1* which are commonly overexpressed by cancers as a survival mechanism. AZD4573 induces apoptosis in cancer cells that are dependent on either MCL1, BFL1 or both proteins for survival (Cidado et al 2020).

Haematological malignancies exhibit a high frequency of MCL1 dependence, which is consistent with known lineage expression and dependency patterns of Bcl2 family anti-apoptotic proteins during haematopoiesis. Whereas CDK9 and MCL1 inhibitors exhibit similar preclinical activity profiles across leukaemias and myeloma, a number of lymphoma models which are insensitive to *MCL1* inhibition are sensitive to acute CDK9 inhibition. This is due to additional dependence on, and AZD4573-mediated modulation of, BFL1 in lymphomas (Boiko et al 2020). BCL2A1, the gene encoding *BFL1*, is a target of NF-κB signalling, which is frequently dysregulated in many lymphomas, including PTCL and cHL.

CCI [redacted]

Figure 2 CCI

CCI
CCI
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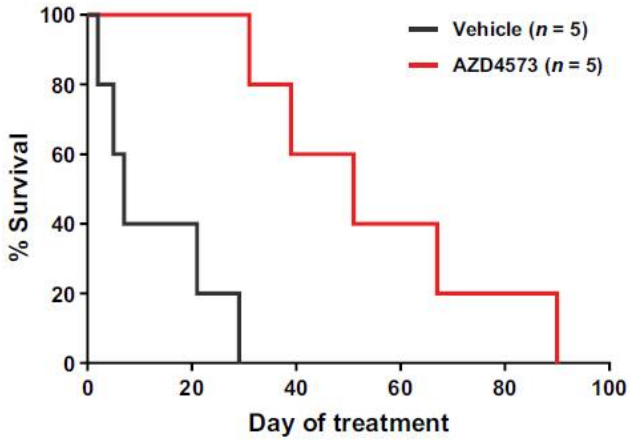
CCI

Figure 3 CCI

CCI
CCI

Furthermore, in a patient-derived xenograft model of angioimmunoblastic T-cell lymphoma, 4 cycles of AZD4573 markedly improves survival of the animals (Cidado et al 2020).

Figure 4 Effect of AZD4573 on OS in Angioimmunoblastic T-cell Lymphoma Patient-derived Xenograft Model (DFTL-78024; n = 5)



Abbreviations: n, number; OS, overall survival.
Source: Cidado et al 2020

Module 1 of this study explores AZD4573 monotherapy in these patient populations; if monotherapy treatment shows anti-tumour efficacy in r/r PTCL or r/r cHL, AZD4573 may be investigated in combination with other anti-cancer agents for greater efficacy. In this case, combination therapy modules will be added to the study via a protocol amendment.

The overarching primary hypothesis for this study is: AZD4573 will demonstrate anti-tumour efficacy, as monotherapy or in combination with other anti-cancer agents, in participants with either r/r PTCL or r/r cHL.

2.2 Background

Peripheral T-cell lymphomas represent a small heterogeneous subgroup of non-Hodgkin lymphomas (Swedlow et al 2017). Approximately 80000 new cases of non-Hodgkin lymphoma are diagnosed annually in the United States (Cancer Stat Facts: Non-Hodgkin Lymphoma) and 123000 cases annually in Europe (GLOBOCAN 2020). Less than 10% of these cases are PTCL (Armitage et al 2004). There are > 20 subtypes of PTCL and the main subtypes are: PTCL not otherwise specified (~30%), angioimmunoblastic T-cell lymphoma (AITL; 15% to 30%), anaplastic large cell lymphoma (ALCL; ~15%), and natural killer T-cell lymphoma (NKTCL; ~10%; Fiore et al 2020). Notably, the incidence of PTCL and proportion of subtypes differ across global regions. Of 240000 cases of non-Hodgkin lymphomas diagnosed annually in Asia (GLOBOCAN 2020), 15% to 30% are classified as PTCL. Hence, in contrast to the US and Europe, NKTCL is the major PTCL subtype in Asia (Park and Ko 2014).

Most PTCL patients progress after receiving first line chemotherapy-based protocols, with or without auto-HSCT. Currently, 3 drugs are approved (as accelerated approvals) by the FDA

for use in all subtypes of r/r PTCL: pralatrexate (a novel antifolate agent); romidepsin; and belinostat (histone deacetylase inhibitors). Of these, pralatrexate and romidepsin are also approved in Japan (along with several other therapies approved on the basis of single-arm trial data); and none are approved in the EU. None of these drugs provide a cure and the ORR is only 25% to 30% (Zain 2019). In addition, the anti-CD30 antibody-drug conjugate BV is approved for relapsed ALCL or CD30+ PTCL in the United States, EU, and Japan, based on an ORR of 86%. Patients with r/r PTCL, including patients with ALCL relapsing after BV, have limited treatment options and poor outcomes underscoring the high unmet medical need in these patient populations.

Classical Hodgkin Lymphoma (cHL) is a unique haematopoietic neoplasm characterised by cancerous Reed Sternberg cells. Approximately 9000 new cases of HL present each year in the US, ~20000 in Europe, and ~14000 in Asia (GLOBOCAN 2020). In HL the cure rate is high, which is reflected by a 5-year OS after initial diagnosis of 80% to 90% (Cancer Stat Facts: Hodgkin Lymphoma.). Historically, treatment has been based on chemotherapy and radiotherapy in first line and adding auto-HSCT in second line treatment. In recent years, BV and the anti-PD1 check point inhibitors nivolumab and pembrolizumab have been introduced as new approved treatments for cHL in the US (nivolumab under accelerated approval), EU, and Japan. Although these novel treatments have demonstrated high response rates, the majority of r/r cHL patients do not achieve durable remission and go on to develop progressive disease, highlighting the continuing need for additional treatments in this patient population (Connors et al 2020; Chen et al 2016; Chen et al 2019; Kuruvilla et al 2021).

AZD4573 (formerly known as AZ13810325) is a potent and selective inhibitor of CDK9 with nanomolar potency against the enzyme (IC50 < 4nM) and excellent selectivity over other CDK family members. AZD4573 decreases pSer2RNAP2 levels (the phosphorylation levels of Ser2 found in the carboxyl-terminus domain of RNA polymerase II [RNAP2]). This decrease in pSer2RNAP2 is linked to preferential reduction of labile proteins like the Bcl2 family anti-apoptotics MCL1 and BFL1 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).

In a first time in human study (Study D8230C00001), the safety and tolerability of AZD4573 monotherapy have been demonstrated in B cell non-Hodgkin lymphoma at the established RP2D of 12 mg 1QW starting with an intra-participant dose ramp-up. Furthermore, anti-lymphoma activity was reported in DLBCL patients. No patients with PTCL or cHL were enrolled in the study.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD4573 is provided in the IB.

2.3 Benefit/Risk Assessment

More detailed information about the known and anticipated benefits and potential risks of AZD4573 may be found in the IB and the relevant modules.

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

2.3.1 Risk Assessment

The safety and tolerability of AZD4573 monotherapy at the established lymphoma RP2D (12 mg 1QW including intra-participant ramp-up) have already been demonstrated in the first time in human study (Study D8230C00001).

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:

Table 2 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Important identified risks: • TLS • Transaminases increase • Bilirubin increase with transaminase (ALT or AST or both ALT and AST) increase • Diarrhoea • Nausea • Vomiting • Neutropenia (includes neutrophil count decreased) • Febrile neutropenia *Important potential* risks: • Gastro-intestinal 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	Risks identified based on nonclinical and clinical data available to date.	These risks are monitored via routine pharmacovigilance activities and standard treatment practices. Further details of these risks can be found in the AZD4573 IB. Risk minimisation activities are reflected in the study protocol specific inclusion and exclusion criteria, alongside the safety monitoring strategy (Section 8), dose modification guidance (Section 6.6), toxicity management guidelines (per module), and concomitant medication guidance (Section 6.5). Additionally, enrolled participants will have been screened for adequate bone marrow function prior to commencing AZD4573 as per the exclusion criteria in the protocol.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TLS, tumour lysis syndrome.

For a complete characterisation for each risk please refer to the IB for AZD4573.

In general, the protocol includes measures such as frequent monitoring of blood counts and serum chemistry, along with other additional monitoring. A urine dip stick test will be also be performed, where a positive test will trigger urine microanalysis for the presence of casts (red cell and protein casts). For a summary of management for each risk, including dose modifications, see Section 6.6 and the Dose Modification section of the relevant module.

In addition to these risks, embryo-foetal and reproductive toxicity is *Missing information* in relation to AZD4573.

No reproductive toxicology or teratogenic studies have been conducted with AZD4573 to date, and it is unknown whether the drug is excreted in human milk. Therefore, WOCBP and men should agree to use highly effective contraception as specified in Section 5.1, and women who are breast feeding 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 pregnancy test before receiving IP.

AstraZeneca has procedures in place to ensure that new or emerging, important clinical safety findings are handled in accordance with a global best practises. 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 "ICH E2A Clinical Safety Data Management: Definitions and standards for reporting", which provides guidance to support that serious unexpected adverse drug reactions information must be provided as early as early as possible, but no later than 7 days (fatal/life threating event) or otherwise 15 days.

Safety issues may arise during or after a participant has completed the trial. Important clinical safety issues are those findings that might adversely influence the benefit-risk assessment of a medicinal product. Upon review of such findings, AstraZeneca may decide to communicate the finding in an expedited manner, so that investigators can manage participants accordingly and ensure that a positive risk benefit is maintained. AstraZeneca commits that any changes to the dosing, dose schedule, or any aspect of participant care, as a result of any new or emerging clinical safety finding, are handled in a way that is consistent with global best practises.

The majority of toxicities observed with 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 toxicities are manageable with appropriate prophylaxis and treatment, and by dose modification.

Regarding the hepatic toxicity events, it has been observed that whilst 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 severe hepatic injury (see the AZD4573 IB). 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 does not lead to adverse clinical sequelae or consistent increase in severity of events.

The safety and tolerability of AZD4573 monotherapy at the established lymphoma RP2D (12 mg 1QW including intra-participant dose ramp-up) have already been demonstrated in the first time in human study (Study D8230C00001).

2.3.2 Benefit Assessment

AZD4573 has the potential to provide clinical benefit in terms of anti-tumour efficacy, as monotherapy and in combination with other anti-cancer treatments, in participants with relapsed/refractory PTCL or cHL.

Nonclinical studies support the hypothesis that inhibiting CDK9 may be a valid target for the treatment of haematological malignancies including lymphomas (Section 2.1). Furthermore, preliminary anti-tumour activity has been observed with AZD4573 as monotherapy in participants with relapsed or refractory haematological malignancies in the ongoing FIH, Phase I dose escalation study (Study D8230C00001). Best objective responses included 1 CR, 1 PR, and 4 SD in 17 dosed participants with DLBCL. Signs of clinical activity were also observed in participants with other haematological malignancies, such as CLL, AML, and MM.

In patients with r/r PTCL who have limited treatment options and patients with r/r cHL who have exhausted standard of care and not achieved remission, the potential clinical benefits with AZD4573 warrant investigation, as current preclinical data suggest that AZD4573 is an attractive investigational drug for these diseases.

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

2.3.3 Overall Benefit: Risk Conclusion

The safety and tolerability of AZD4573 monotherapy (RP2D 12 mg 1QW including intra-participant dose ramp-up) have already been demonstrated in lymphoma patients in the first time in human study (Study D8230C00001).

Furthermore, taking into account the measures taken to minimise risk to participants in the current study, including specific monitoring and dose modification criteria specified in the protocol for cases of transaminase +/- bilirubin increase, the safety risks identified in association with AZD4573 are justified by the anticipated benefits that may be afforded to participants with r/r PTCL or r/r cHL.

The benefit-risk assessment for AZD4573 in combination with other anti-cancer therapies will be addressed in individual study modules following their addition by protocol amendment.

Please see Section 2.3.4 for the benefit/risk assessment pertaining to the conduct of this study during the COVID-19 pandemic.

2.3.4 Benefit/Risk Pertaining to AZD4573 Study Conduct During the COVID-19 Pandemic

Cancer patients have an increased risk of exposure to SARS-CoV-2 due to frequent hospital or clinic visits for treatment and monitoring. A retrospective cohort study of 28 SARS-CoV-2 (COVID-19)-infected cancer patients from 3 hospitals in Wuhan, China, reported that a third of patients (28.6%; N = 8) were suspected to have acquired the infection by hospital-associated transmission (Yu et al 2020, Zhang et al 2020). Patients with cancer may have a higher risk of developing COVID-19 than individuals without cancer but current evidence appears insufficient to support a conclusive association between cancer in general and COVID-19 (Kumar et al 2019, Xia et al 2020).

This Phase II study will enrol participants with r/r PTCL and r/r cHL. Participants in this study will receive AZD4573, which leads to inhibition of CDK9. In Module 1, they will not be receiving chemotherapy, radical radiotherapy, immunotherapy, or other continuing antibody treatments for cancer as part of the treatment strategy. Overall, the study treatment and procedures received during the course of this study are considered to have low risk for increasing susceptibility to COVID-19 infection.

Furthermore, this study population would typically have frequent healthcare-related clinic visits, irrespective of the participation in a study. Therefore, it is anticipated that overall, participation in this clinical study should not significantly increase this population's risk of exposure to COVID-19 infection.

The scheduled safety monitoring with increased clinic visits compared to standard of care monitoring are intended to protect participants in the study, but there may be increased risk to participants by exposure to SARS-CoV-2 due to study visits. However, this risk is offset by the benefit that participants may receive in the form of an extended period of PFS.

In accordance with EMA and FDA guidelines (EMA-CTFG-EC 2021, FDA 2020), 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 study 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.

If there is a need to reconsent study participants for the implementation of new urgent changes in study conduct, additional guidance on alternative means of obtaining reconsent to avoid unnecessary study visits is provided as Appendix H 1 (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/IECs in line with relevant local guidance and procedures.

3 OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints

Type	Objectives	Endpoints
Primary		
Efficacy	To assess the efficacy of the module-defined study treatment in participants with either r/r PTCL or r/r cHL by evaluation of objective response rate.	Refer to modules for endpoints
Secondary		
Efficacy	To assess the efficacy of the module-defined study treatment in participants with either r/r PTCL or r/r cHL.	Refer to modules for endpoints
Safety	To assess the safety and tolerability of the module-defined study treatment.	Adverse events, laboratory data, vital signs, and ECG changes. Assessments related to AEs cover: • Occurrence/Frequency • Relationship to IP as assessed by investigator • CTCAE grade • SAEs • Death • AEs leading to discontinuation of IP • AEs leading to dose modifications • AESIs
PK	To assess the plasma/serum PK of AZD4573 and/or other module defined anti-cancer agents when given in combination (as applicable).	• Plasma concentrations and derived PK parameters for AZD4573 (and/or other module defined anti-cancer agents given in combination)

Table 3 Objectives and Endpoints

Type	Objectives	Endpoints
Exploratory		
PD	To assess the pharmacodynamics of AZD4573 and other module-defined anti-cancer agents when given in combination.	Refer to Modules for endpoints
CCI	CCI	• CCI
Genetics	To collect and store CCI sample, for future exploratory research CCI CCI	CCI

Abbreviations: AE, adverse event; AESI, adverse event of special interest; cHL, classical Hodgkin Lymphoma; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; IP, investigational product; PD, pharmacodynamics; PK, pharmacokinetics; PTCL, peripheral T-cell lymphoma; SAE, serious adverse event.

4 STUDY DESIGN

4.1 Overall Design

This is a modular, Phase II, multicentre, open-label, dose confirmation and expansion study in participants with r/r PTCL or r/r cHL.

The modular design of this study allows evaluation of AZD4573 as monotherapy or in combination with other anti-cancer agents. The core study design is to establish the efficacy of AZD4573, administered as monotherapy or combination therapy, to participants with either r/r PTCL or r/r cHL and to confirm the safety profiles and PK in these populations.

This study will use the established RP2D of AZD4573 for lymphoma, as assessed in the ongoing Phase I monotherapy study of AZD4573 (D8230C00001). The RP2D for lymphoma is 12 mg weekly, starting with an intra-participant dose ramp-up. This dose will not be exceeded during the study.

Further modules may be added via protocol amendment. Study information applicable to all participants in this study is described in the core sections of this protocol; the rationale for each study treatment and cohort, and specific study information and assessments will be described in each separate module. This study is planned to take place in approximately 30 centres across 10 countries.

Module 1 will assess the efficacy, safety, tolerability, and PK of AZD4573 as a monotherapy in r/r PTCL and r/r cHL populations and explore pharmacodynamics in these disease subtypes. If AZD4573 monotherapy is found to have promising anti-tumour efficacy in Module 1, an AZD4573 monotherapy Phase II expansion may be added via a substantial protocol amendment. Additional modules may also be added via substantial protocol amendments to assess AZD4573 in combination with other anti-cancer agents in r/r PTCL or r/r cHL based on emerging preclinical and clinical data and study rationale.

Future modules may include an initial combination dose confirmation phase, dependent on the AZD4573 combination partner being evaluated. The planned intra-participant dose escalation, the cohort escalation scheme, and the dosing schedule may be amended in light of emerging PK, safety, pharmacodynamic data and available efficacy data, which will be reviewed on an ongoing basis throughout the study.

- A study-specific SRC will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety, PK, and other relevant data (see study design section of the relevant module).
- The end of module is defined as the last scheduled visit or contact of the last participant enrolled in the module (Section 4.4).
- The end of the study is defined as the last visit of the last participant undergoing the study, or as the last scheduled procedure shown in the relevant module's SoA for the last participant in the study globally (Section 4.4).

4.1.1 Modular Protocol Structure

The structure of the protocol will also follow a modular design. Information relating to the overall study, including study objectives, rationale, core inclusion and exclusion criteria, safety assessments, and AE reporting can be found in this core protocol module (ie, Sections 1 to 9).

The starting dose/schedule of AZD4573 in further combination modules will not exceed the equivalent maximum dose of AZD4573 found to be tolerated in the monotherapy Module 1 or from other studies in the clinical programme at that point.

Study drug-specific information including doses and justifications, toxicity management, dose

modifications, and concomitant medications can be found in the relevant module.

4.1.2 Module Naming Conventions

The study will consist of 1 initial module (Module 1) evaluating the efficacy, safety, and tolerability of AZD4573 as monotherapy in participants who have either r/r PTCL or r/r cHL. Additional modules may be added by substantial amendment evaluating AZD4573 in combination with other anti-cancer agents in the r/r PTCL or r/r cHL population.

Table 4 Module Naming Conventions

Module	Tumour type	Intervention
Module 1 – Monotherapy	r/r PTCL r/r cHL	AZD4573
Naming convention for potential combination therapy modules[a]		
Module X – AZD4573 + [combination treatment]	r/r PTCL	AZD4573 + [combination treatment]
Module Y – AZD4573 + [combination treatment]	r/r cHL	AZD4573 + [combination treatment]

[a] Anticipated combination treatment modules will be numbered per the order added to the study protocol (Module 1, Module 2, Module 3, ect). The order of addition of the combination treatment modules is to be determined based on clinical and nonclinical data.

Abbreviations: cHL, classical Hodgkin Lymphoma; PTCL, peripheral T-cell lymphoma; r/r, relapsed/refractory.

4.1.3 Regulatory Amendment for Additional Modules

New modules may be added in the future to assess treatment combinations in either r/r PTCL or r/r cHL. Up to 5 additional combination modules may be added. The combination partners may include, but are not limited to, the following options: romidepsin, belinostat, pralatrexate, anti-PD1, and BV.

To support amendment of the protocol for additional modules/cohorts, AstraZeneca will provide a summary of all nonclinical and clinical data to support the cohort expansion or any new proposed combination treatment 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 any 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 patient population to be enrolled in the cohort/module, if the population will be selected based on a diagnostic assay.

4.1.3.1 Europe and Rest of World

AstraZeneca will provide a substantial amendment for review and approval.

4.1.3.2 United States of America

AstraZeneca will provide an amendment to the FDA 60 days in advance of planned enrolment in a module for any combination involving a drug for which the recommended Phase II dose has not been determined for the proposed dosage regimen to be employed, or at least 30 days in advance of a planned enrolment in a module for drugs where the recommended Phase II dose has been determined for the proposed dosage regimen to be employed. AstraZeneca will begin enrolment of participants into that module in the United States after IRB approval.

4.1.4 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases 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) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining reconsent for the mitigation procedures (note, in the case of verbal reconsent, the ICF should be signed at the participant's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.
- Home or Remote visit: Performed by a site qualified HCP or HCP provided by a TPV.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home IP administration: Performed by a site qualified HCP, HCP provided by a TPV, or by the participants or the participant's caregiver, if possible and appropriate for the therapy. Additional information related to the visit can be obtained via telemedicine.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix H.

4.2 Scientific Rationale for Study Design

This is a modular, Phase II, multicentre, open-label, dose confirmation and expansion study primarily designed to establish the efficacy of AZD4573, administered as monotherapy or combination therapy, to participants with either r/r PTCL or r/r cHL. The study will also confirm the safety profile and PK of the module-defined AZD4573 monotherapy or combination therapy in these populations, and explore potential biological activity by assessing CCI [redacted] pharmacodynamics for anti-tumour efficacy. Module 1 will assess the efficacy of AZD4573 as a monotherapy in r/r PTCL and r/r cHL populations.

If AZD4573 monotherapy is found to have promising anti-tumour efficacy in Module 1, an AZD4573 monotherapy Phase II expansion may be added via a substantial protocol amendment. Additional modules may also be added via substantial protocol amendments to assess AZD4573 in combination with other anti-cancer agents in r/r PTCL or r/r cHL based on emerging preclinical and clinical data and study rationale. Future modules may include an initial combination dose confirmation phase, dependent on the AZD4573 combination partner being evaluated. The planned intra-participant dose escalation, the cohort escalation scheme, and the dosing schedule may 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 results from this study will form the basis for decisions for future studies. Biological samples will be collected in order to establish an archive and allow future meta-analysis of data derived from a number of studies with AZD4573.

The statistical rationale for the study design and sample size criteria are provided in the respective modules.

4.3 Justification for Dose

Information on dose justification is provided in the respective modules.

4.4 End of Study Definition

A participant is considered to have completed the study if they have completed all parts of the study including the last visit or the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study globally. The end of module is defined as the last scheduled visit or contact of the last participant enrolled in the module; see the relevant module for more information.

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

5 STUDY POPULATION

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

All criteria and considerations listed in this section are for the core study design and apply to all modules of the study. Additional, module-specific criteria and considerations are listed in the study population section of the relevant module.

5.1 Inclusion Criteria

The below are the core inclusion criteria for all modules of the study; all participants must meet the criteria described in the relevant module in addition to those described below. Where module-specific criteria are more stringent than core study criteria, the module-specific criteria take precedent.

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

Informed Consent

1 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
2 Provision of signed and dated, written informed consent prior to any mandatory study-specific procedures, sampling, and analyses.

3 Provision of signed and dated written Optional Genetic Research Information ICF is required prior to collection of samples for optional genetic research that supports the Genomic Initiative.

Age

4 Participant must be at least 18 years of age inclusive at the time of signing the informed consent.

Type of Participant and Disease Characteristics

5 Participants who are diagnosed with one of the following, as defined by the World Health Organisation:
   (a) Peripheral T-cell Lymphoma
   (b) Classical Hodgkin Lymphoma

6 Eastern Cooperative Oncology Group performance status of ≤ 2.

7 Must have received at least 1 prior line of therapy for the treatment of current disease and have documented relapsed or refractory active disease requiring treatment, defined as:
   (a) Recurrence of disease after response to prior line(s) of therapy, or
   (b) Progressive disease after completion of or on the treatment regimen preceding entry into the study, or
   (c) Disease which did not achieve an objective response (CR or PR).

8 Prior lines of therapy:
   (a) PTCL: Participants must have failed at least 1 prior therapy for the treatment of PTCL.
      (i) Non NK-PTCL: Prior therapy must have included an alkylating agent and/or anthracycline. In addition, ALCL participants must have received BV as part of prior therapy.
      (ii) NKTCL: Prior treatment must have included asparaginase and/or a platinum agent.
   (b) cHL: Participants must have failed at least 2 prior therapies for the treatment of cHL (including BV and anti-PD1) except where unable to receive BV or anti-PD1 due to neuropathy or autoimmune disease.

9 Presence of at least 1 radiographically measurable, FDG-avid lymphoma disease lesion > 1.5 cm (according to the Lugano criteria [Cheson et al 2014]).

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

11 Willing and able to participate in all required evaluations and procedures in this study protocol including receiving IV administration of study drug and being admitted, if required, for at least 24 hours during study drug administration.

12 Fresh tumour tissue or archival tumour tissue must be confirmed to be available at screening.

13 Adequate haematologic function at screening (Table 5).

(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 lab assessment.

Table 5 Criteria for Adequate Haematological Function

Category	Parameter	Value
Haematologic	Haemoglobin	≥ 8.0 g/dL
	Absolute neutrophil count	≥ 1000 cells/mm3 (1.0×10^9/L)
	Platelet count	≥ 75000 cells/mm3 (75×10^9/L) without bone marrow involvement
		≥ 50000 cells/mm^3 (50×10^9/L) with bone marrow involvement

14 Adequate organ function at screening as defined below in Table 6.

Note that 1 rescreen is permitted for participants if required, in line with Section 5.4.

Table 6 Criteria for Adequate Organ Function

Category	Parameter	Value
Hepatic	Bilirubin	≤ 1.5 × ULN in the absence of Gilbert's syndrome[a] ≤ 3 × ULN if the participant has Gilbert's syndrome[a]
	Alanine transaminase and aspartate transaminase	≤ 3 × 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 × ULN and no ongoing pancreatitis
	Amylase	≤ 3 × ULN and no ongoing pancreatitis
Cardiac	LVEF as assessed by echocardiography MUGA[b]	≥ 40%

[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, multi-gated acquisition scan; ULN, upper limit of normal.

15 **PTCL Only:** All participants with PTCL must be willing and able to provide mandatory baseline bone marrow aspirate and/or biopsy no older than 3 months, and agree to undergo post-treatment bone marrow biopsy when required to confirm response.

Reproduction

16 Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

(a) Male participants:

(i) Male participants must be willing to use barrier contraception (ie, condoms) for the duration of the study plus a further 4 months after discontinuing AZD4573. Non-pregnant WOCBP partners of male participants should use highly effective methods of contraception (defined below) for the duration of the study and for a washout period of 4 months after discontinuing AZD4573.

(ii) 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.

(b) Female participants:

(i) Female participants must be either women not of childbearing potential (defined below), or must use one highly effective form of birth control (defined below) from 3 months prior to enrolment (the participant should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study), throughout the study, and until 7 months after last dose of study intervention.

(ii) All WOCBP must have a negative serum pregnancy test result at Visit 1.

(iii) 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.

* Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to first dose of study drug without an alternative medical cause. The following age-specific requirements apply:

* Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the postmenopausal range.
* Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

(iv) Women of childbearing potential must use 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 who are sexually active with a non-sterilised male partner must agree to use 1 highly effective method of birth control, as defined below, from enrolment throughout the study and until at least 7 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

(v) Highly effective birth control methods include: sexual abstinence (note that periodic abstinence methods are not acceptable methods of contraception [eg, calendar, ovulation, symptothermal, post-ovulation methods, declaration of abstinence for the duration of exposure to IMP, and withdrawal)], a vasectomised partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

Genomics Initiative Research Study (Optional):

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

(a) Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic 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.

Bone Marrow Aspirate / Tumour Biopsy at Progression (Optional):

18 For inclusion in the optional bone marrow aspirate/tumour biopsy component of the study, participants must fulfil the following additional criteria:

(a) Provision of signed, written, and dated informed consent for a bone marrow aspirate or tumour biopsy at disease progression. If a participant declines to participate in the bone marrow aspirate/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.

(b) 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.

5.2 Exclusion Criteria

The below are the core exclusion criteria for all modules of the study; all participants must meet the criteria described in the relevant module in addition to those described below. Where module-specific criteria are more stringent than core study criteria, the module-specific criteria take precedent.

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

Type of Participant and Disease Characteristics

1 **PTCL only**: Presence of bulky disease (defined as largest lymphoma lesion ≥ 10 cm) or a LDH value > 3 x ULN.

2 **PTCL only:** Diagnosis of any of the following:

(a) Lymphoblastic/precursor T-cell lymphoma or leukaemia

(b) T-cell prolymphocytic leukaemia

(c) T-cell large granular lymphocytic leukaemia

(d) Cutaneous T-cell lymphoma (eg, primary cutaneous type ALCL, mycosis fungoide/Sezary syndrome).

Medical Conditions

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

4 Presence of, or history of, CNS lymphoma, leptomeningeal disease, or spinal cord compression.

5 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 1 year prior to 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.

6 As judged by the investigator, any evidence of:

(a) Severe or uncontrolled systemic disease (eg, severe hepatic impairment, interstitial lung disease [bilateral, diffuse, parenchymal lung disease]).

(b) Current unstable or uncompensated respiratory or cardiac conditions.

(c) Uncontrolled hypertension.

(d) 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).

(e) IV anti-infective treatment within 1 week before first dose of study drug.

7 Known history of infection with HIV.

8 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 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.

9 Any of the following cardiac criteria:

(a) Resting QT interval corrected using Fridericia's formula (QTcF) ≥ 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 (e.g., 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.

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) CHF (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 ischemic attacks or any other CNS bleeding.

Prior/Concomitant Therapy

12 Treatment with any of the following:

(a) Received major surgery (as defined by the investigator) or immunotherapy (specifically immune checkpoint inhibitors) within 28 days.

(b) Received cytotoxic chemotherapy, standard anti-lymphoma therapy, or radiation therapy within 14 days of receiving the first dose of study treatment.

(c) Received adoptive cellular therapy such as autologous or donor NK cell or T lymphocyte infusions [eg, CAR-T cells]) within 90 days.

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

(e) Participants who have previously received an autologous 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.

(f) Participants with a history of allogeneic SCT are excluded UNLESS the following eligibility criteria are met:

(i) Transplant was > 180 days prior to the first scheduled dose

(ii) Participant has no history of liver GVHD

(iii) Participant has no active GVHD

(iv) Participant has not taken immunosuppressive medications for at least 1 month prior to first scheduled dose; low-dose steroids (≤ 10 mg of prednisone or equivalent per day) are permitted as therapy for comorbid conditions other than GVHD.

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, but use of corticosteroids as therapy for lymphoid cancer is not permitted. Short courses of steroids before study entry are allowed. During study participation, participants may 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).

Prior/Concurrent Clinical Study Experience

15 Participation in another clinical study with an IP administered in the last 5 half-lives of that IP.

16 Participants with a known hypersensitivity to AZD4573 or any of the excipients of the product.

Other Exclusions

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

18 Judgment 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.

19 Previous enrolment in the present study.

20 For women only - currently pregnant (confirmed with positive pregnancy test) or breastfeeding.

5.3 Lifestyle Considerations

There are no dietary/activity restrictions for this study. For restrictions around reproduction and contraception, refer to the inclusion criteria (Section 5.1).

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 CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Only 1 rescreening is allowed in the study. Rescreened participants should be assigned the same participant number as for the initial screening.

6 STUDY INTERVENTION

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

6.1 Study Intervention(s) Administered

Please refer to the relevant module for information on study intervention(s).

6.2 Preparation/Handling/Storage/Accountability

1 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.

2 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.

3 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).

4 Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

5 The study personnel at the investigational site will account for all study intervention dispensed and where appropriate, for all destruction of study intervention or delivery of intervention to sponsor for destruction. Unused study intervention 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.

6.3 Measures to Minimise Bias: Randomisation and Blinding

This is an open-label study. Each potential participant is assigned a unique participant enrolment number. If a participant withdraws from the study, then the enrolment number cannot be reused. Study intervention will be dispensed at the study visits summarised in the relevant module. Returned study intervention should not be re-dispensed to the participants.

If an unscheduled assessment is performed, and the participant has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed to minimise any unintentional bias caused by some participants

being assessed at a different frequency than other participants.

6.4 Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When 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.

6.5 Concomitant Therapy

Information on any medication or vaccine that the participant is receiving at the time of enrolment, or has received in at least the 30 days before starting IP, as well as all concomitant treatments given during the study (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) must be recorded in the eCRF along with:

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

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Given the proposed clinical dosing regimen of AZD4573, an 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. No AEs suggestive of a drug-drug interaction have been reported so far in clinical studies with AZD4573. Pharmacokinetic drug interaction data based on in vitro studies only is available in the IB.

Prohibited concomitant therapies are listed in Table 7 and permitted concomitant therapies are listed in Table 8. Concomitant medication additional to those listed in Table 8 may be considered on a case-by-case basis by the investigator in consultation with the Study

Physician if required.

Table 7 Prohibited Concomitant Therapies

Prohibited medication/class of drug	Usage
Any other investigational therapy (including anticancer therapy, other than those under investigation in this study.)	Should not be given concomitantly while the participant is on study intervention.
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study.	Should not be given concomitantly while the participant is on study intervention. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy].)
Live attenuated vaccines	Should not be given through 30 days after the last dose of investigational products.
Immunosuppressive medications such as methotrexate, azathioprine, and tumour necrosis factor-α blockers.	Should not be given concomitantly or used for premedication.

Table 8 Permitted Concomitant Therapies (Conditional)

Supportive medication/class of drug	Usage
Premedication for prophylaxis of diarrhoea, nausea, vomiting, TLS, and infection.	Permitted as per protocol and as deemed required by the investigator.
Blood transfusions	During the study, blood and platelet transfusions are allowed as clinically indicated at any time during the study and can be given as per local institutional guidelines.
G-CSF	G-CSF should not be used prophylactically from Cycle 1, Day 1 but can be started when medically indicated.
Corticosteroids	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.

Table 8 Permitted Concomitant Therapies (Conditional)

Supportive medication/class of drug	Usage
Concomitant drugs that have the potential to prolong QTc	Concomitant drugs that have the potential to prolong QTc should not be used around the time of the scheduled ECG assessments during this study.
Strong CYP3A4 inducers/inhibitors	It is recommended that treatment with strong CYP3A4 inducers is avoided, unless it is deemed clinically warranted in the opinion of the investigator. 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 should be administered 8 to 12 hours after the completion of the AZD4573 infusion, if deemed clinically warranted in the opinion of the investigator.
Best supportive care (including recombinant growth factor support, bisphosphonates, antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc].)	Should be used, when necessary, after discussion with the study physician and in accordance with local institutional guidelines.
Inactivated viruses, such as those in the influenza vaccine and COVID-19 vaccines.	The sponsor recommends avoiding administering COVID-19 vaccinations during the 72 hours prior to administration of the first dose of IP, or during Cycle 1, to avoid biases in the interpretation of safety data due to the potential overlap of vaccine-related AEs with IP AEs.

Abbreviations: AE, adverse event; ECG, electrocardiogram; G-CSF, granulocyte colony stimulating factor; IP, investigational product; SAE, severe adverse event; TLS, tumour lysis syndrome.

6.6 Dose Modification

If, in the opinion of the investigator, a participant experiences a clinically significant and/or unacceptable adverse reaction, then the dose may be temporarily or permanently halted or reduced.

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

See the relevant module for detail on dose modification.

6.7 Intervention after the End of the Study

No intervention is planned after the end of the study. However, provisions will be in place for participants 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. Such participants will continue to be monitored for all SAEs up to 30 days after the last dose of the intervention therapy.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, participants currently receiving treatment with study intervention may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visits and assessments per its protocol. Any participant who would be proposed to move to such a study would be asked to sign a new ICF.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and efficacy during the 30-day follow-up period (Section 8.2.1), or until documented disease progression during the long term follow-up period (Section 8.2.2). See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study.

The participant should continue attending subsequent study visits and data collection should continue according to the study protocol. If the participant does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the participant for the follow-up visit, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A participant who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

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

- Objective disease progression assessed by investigator
- Adverse event as defined in Section 8.3
- Participant or investigator decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment
- Pregnancy (See Section 8.3.10)

- Non-compliance with the CSP (investigator or participant)
- Participant incorrectly initiated on study treatment
  - When the reason does not impact safety, the Study Physician together with the investigator will consider the risk/benefit to the participant of stopping treatment.
  - The Study Physician is responsible for ensuring all such contacts are appropriately documented.
- Unexpected, significant, or unacceptable risk to the participants enrolled in the study.
- Sponsor termination of study for reasons including but not limited to unfavourable risk/benefit or change in drug development plan.

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

Restarting of study intervention may only occur in line with the dose modification and discontinuation guidelines described in the relevant module. Participants who have had investigative treatment discontinued for safety reasons may not be restarted on this treatment during the study.

7.1.1 Criteria for stopping or pausing the study recruitment

At any time point during the trial, the study recruitment may be paused if at least one of the following events occurs:

- Fatal event deemed related to study therapy by the Sponsor and in discussion with the SRC (probable or certain causality based on WHO-UMC after full etiological work-up). This will also result in a comprehensive review of safety.
- Confirmed true Hy's law event as assessed by the Sponsor and in discussion with the SRC.
- A CTCAE grade 4 or higher TLS event that is not reversible within 48 hours as assessed by the Sponsor and in discussion with the SRC.
- Unexpected and life-threatening non-haematological event deemed related to study therapy by the Sponsor and in discussion with the SRC.
- Sponsor decision that study participants are placed at undue safety risk.
- Sponsor decision to discontinue the development of the study treatment in the proposed indications.

If, on an ongoing basis, > 25% of participants experience any AEs related to study intervention that result in discontinuation of study treatment, the study data will be evaluated by the SRC. Enrolment may be paused until the safety data review by the SRC has been completed.

7.2 Participant Withdrawal from the Study

All participants will be followed for survival until death, lost to follow-up, sponsor 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. This is expected to be uncommon.
- 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).
- 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.

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

In addition, participants will be withdrawn from the study in the event that the sponsor terminates this study.

7.3 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.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA for the relevant 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 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 maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, is not anticipated to exceed 436.5 mL in Cycle 1 (cycle duration of 5 weeks) and 124 mL in each subsequent cycle (cycle duration of 3 weeks). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- All efficacy assessments should continue until progression, including when a participant's study treatment has been stopped.

8.1 Efficacy Assessments

Efficacy assessments are detailed in the relevant module.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the relevant module.

8.2.1 30-Day Follow-up Visit

A follow-up visit will be performed 30 (± 7) days from the time that all study intervention is permanently discontinued (see the SoA for the relevant module). Tumour assessments (including PET-CT) will be repeated at this visit if they have not been performed within 9 weeks if the participant discontinued before Week 26, or 12 weeks if the participant discontinued after Week 26.

8.2.2 Long-term Follow-up Visit

Participants who discontinue all study intervention before documented disease progression will be followed according to standard of care until documented disease progression. Disease progression or start of new anticancer 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 LTFU may be performed via phone call. LTFU visits will cease at disease progression. The long-term follow up will not apply to participants who withdraw consent or are lost to follow-up.

8.2.3 Survival Follow-up

All participants will be followed for survival until death, lost to follow up, AstraZeneca closes study, or withdrawal of consent, whichever occurs first. Participants will be followed for survival by telephone calls or clinic visits approximately every 3 months. During this period, information will be collected in the eCRF on survival status and any new anticancer therapies, and on any SAEs considered related to study drug(s) or study procedures.

8.3 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 and an SAE can be found in Appendix B.

Adverse events 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.

All AEs (including SAEs) must be entered into the Clinical Database which will be used to generate the CSR. SAEs are also to be entered into the Global Patient Safety database which is used for expedited and periodic regulatory safety reporting and safety surveillance activities. Regular reconciliation of SAEs between these 2 databases will be conducted by the clinical team as per the Reconciliation Plan on a periodic basis.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs will be collected from time of signature of the ICF, throughout the treatment period and including the follow-up period of 30 days (± 7 days) after last dose of study intervention.

A formal assessment of AEs will occur at the visits marked in the SoA of the relevant module, but AEs reported at any time during the study must also be recorded in the eCRF.

If the investigator becomes aware of a SAE with a suspected causal relationship to the IMP(s) that occurs after the end of the clinical trial in a study participant, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last assessment 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.

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

Adverse event variables

The following variables will be collected for each AE:

- AE (verbatim)
  - The capture of diagnoses is preferred over all associated signs and symptoms. For example: laboratory TLS, clinical TLS, cytokine release syndrome. Provisional diagnoses (eg, PHL) must be updated as soon as possible.
- The date when the AE started and stopped
  - When the onset of an AE in relation to dosing is rapid, for example TLS, it is important to record the **exact time of the start of infusion** dosing and the **time of AE onset** in addition to the dates.
- CTCAE grade/changes in CTCAE grade
- **For TLS events:** Adverse events of TLS shall be graded according to CTCAE. The AE verbatim shall discriminate between laboratory and clinical TLS. In addition, TLS events will be graded according to Howard modification of the Cairo-Bishop grading system (see Appendix G) on the TLS monitoring eCRF form.
- Whether the AE is serious or not

- Investigator causality rating against the IP(s) (yes or no)
- Action taken with IP(s) in response to the AE (for example: no action, dose reduced, treatment temporarily stopped, treatment permanently discontinued).
- Outcome of the event

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

- Date AE met criteria for SAE
  - The date of start of first signs and symptoms should be captured together with the date the event became serious.
- Date investigator became aware of SAE
- Reason AE is classified as serious
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed (yes/no)
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between IP and each Adverse Event, 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 to the CSP.

8.3.4 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.

8.3.5 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 physical examinations, laboratory values, vital signs, ECGs or B symptoms 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 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, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

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

8.3.6 Adverse Events of Special Interest

For AESIs associated with combination treatments, see the relevant module.

The following events are AESIs for participants who receive AZD4573 and must be reported to the sponsor expeditiously irrespective of seriousness criteria or causality:

- Neutropenia, including Febrile neutropenia, Neutropenic sepsis, Neutrophil count decrease
- Thrombocytopenia, including Platelet count decrease
- Hepatotoxicity, including PHL, Drug-induced liver injury, Bilirubin increase with transaminase (ALT or AST, or both ALT and AST) increase
- Pyrexia
- TLS

- Myocardial ischaemia

8.3.7 Potential Hy's Law Cases

Cases where a participant shows elevations in liver transaminases and bilirubin levels require further evaluation. Occurrences of AST and/or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN **must be reported as SAEs due to medical significance. The PHL page of the eCRF form must also be completed without delay. The verbatim of 'Potential Hy's Law' is a provisional diagnosis and must be updated as soon as possible. All PHL cases must be reported by the Sponsor to the USA FDA as a SUSAR in an expedited manner (even before all other possible causes of liver injury have been excluded). Please refer to Appendix E for more details.**

For all PHL events, expedited safety reporting is required. The investigator must inform the sponsor as soon as more information is available on the event.

Please refer to the toxicity management and dose modification guidance in the relevant module. Discussions regarding treatment discontinuation due to increased liver transaminases and/or bilirubin increases should be documented. All PHL cases should be captured in the study PHL log by the central study team.

8.3.8 Disease Progression and Disease Under Study

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the treatment is being studied. It may be an increase in the severity of the DUS 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.

Symptoms of DUS are those which might be expected to occur as a direct result of r/r PTCL or r/r cHL. Events which are unequivocally due to DUS should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the study treatment. Death clearly resulting from disease progression should not be reported as an SAE.

8.3.9 Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, then investigators or other site personnel 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 works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

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

For all PHL events, expedited safety reporting is required. The investigator must inform the sponsor as soon as more information is available on the event.

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

If the eCRF system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by an alternative method.

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

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

The reference document for definition of expectedness/listedness is the IB for the AZD4573.

8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for if the pregnancy is discovered before the study participant has received any study intervention.

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.

8.3.10.1 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. 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 anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs.

If any pregnancy occurs in a female participant during exposure to IP or in the 7 months after discontinuing the AZD4573, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.9) 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 paper-based PREGOUT module is used to report the outcome of the pregnancy.

8.3.10.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 4 months following the last dose (see Inclusion Criteria Section 5.1).

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. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly), occurring from the date of the first dose until 4 months after the last dose should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

If a pregnancy occurs in a 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.

8.3.11 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least 1 of the seriousness criteria. New primary cancers are those that are not the primary reason for

the administration of the study intervention and have been identified after the participant's inclusion in this study. They do not include metastases of the original cancer.

8.3.12 Deaths

All deaths that occur during treatment period, including the follow-up period, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the study monitor/physician at the next monitoring visit and should be documented in the relevant eCRF module. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the DUS, the AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the eCRF. The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign single main cause of death together with any contributory causes. Autopsies should be requested if available.
- Death with an unknown cause should always be reported as an SAE, but every effort should be made to establish a cause of death. It should also be documented in the eCRF. A postmortem may be helpful in the assessment of the cause of death, and if performed, a copy of the postmortem results (with translation of important parts into English) should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.
- Deaths that occur after the treatment period during the survival follow-up period should be reported on the survival log on the eCRF. If the death occurred as a result of an event that started after the defined follow-up period and the event is considered by the investigator to be due to a late-onset toxicity to study intervention, then it should also be reported as an SAE.

8.3.13 Medication Error

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.9) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 4.

8.4 Overdose

Overdose information for AZD4573 is below; refer to relevant module for information on overdose for combination therapies.

For this study, any dose of AZD4573 greater than the dose intended to be delivered 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 inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.9) and **within 30 days** for all other overdoses.

For overdoses associated with a SAE, the standard reporting timelines apply.

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.

8.5 Human Biological Samples

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

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

- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic 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.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterisation of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

Refer to relevant module for information on PK.

8.5.2 Pharmacodynamics

Refer to relevant module for information on pharmacodynamics.

8.5.3 Immunogenicity Assessments

Refer to relevant module for information on immunogenicity assessments.

8.6 CCI [redacted]

Refer to relevant module for information on CCI [redacted].

8.7 Optional Genomics Initiative Sample

Collection of optional samples for genomics initiative research is also part of this study as specified in the SoA and is subject to agreement in the ICF addendum. A CCI [redacted] 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. This CCI [redacted] sample will be taken from consenting participants prior to AZD4573 dosing.

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

For storage and destruction of genetic samples see Appendix D.

8.8 Health Economics

Not applicable for study.

9 STATISTICAL CONSIDERATIONS

The statistical analyses will be performed by AstraZeneca or CRO under the direction of the Early Biometrics Oncology, AstraZeneca. A comprehensive SAP will be prepared.

9.1 Statistical Hypotheses

Not applicable.

9.2 Sample Size Determination

Refer to relevant module for information on sample size determination.

9.3 Populations for Analyses

Refer to relevant module for information on populations for analyses.

9.4 Statistical Analyses

The SAP will be finalised prior to database lock and 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. Any deviations from this plan will be reported in the CSR.

9.4.1 General Considerations

Unless stated otherwise, each module and cohort will be analysed separately. Data will be presented by cohort. Descriptive statistics will be used for all variables. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Geometric mean and coefficient of variation may be presented as applicable. Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated from the population total, by cohort and by timepoint as appropriate. Time to event variables will be presented using the KM methodology where appropriate, including median time calculated from the KM curves. SAS® version 9.4 (as a minimum) will be used for analyses presented in the CSR.

Depending on the extent of any impact, summaries of data relating to participants diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study treatment, and other protocol deviations) may be generated. More details will be provided in the SAP.

Refer to the relevant Module for details on analyses and cut-off triggers.

9.4.2 Efficacy Analyses

Analysis of Primary Endpoint (Efficacy)

The primary objective of this study is to assess the efficacy of the module-defined study treatment in participants with r/r PTCL or r/r cHL. Endpoints for this objective are specific to each module.

For information on efficacy analyses and endpoints, refer to the relevant module.

9.4.3 Safety Analyses

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs, and ECG changes. These variables will be collected for all participants. All safety data listings and summaries will be created using the safety analysis set.

Adverse events will be listed individually by cohort and participant. The number of participants experiencing each AE will be summarised by the MedDRA system organ class, MedDRA preferred term, and CTCAE grade (in line with NCI CTCAE Version 5.0). TLS will be graded by CTCAE grade and Howard's modification of Cairo-Bishop grading (Appendix G; Howard et al 2011). The number and percentage of participants experiencing each AE, and the number and percentage of participants with AEs in different categories (eg, causally related and CTCAE Grade ≥ 3) will be summarised by 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.

Adverse event summary tables will include only treatment-emergent AEs. Adverse events 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 the follow-up period (as defined in the individual study Modules), but prior to subsequent cancer therapy. AEs occurring outside of this period will be listed but not summarised.

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 could be 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. Duration of exposure will be summarised.

Haematology, serum chemistry, vital signs, ECG data, and other laboratory values will be listed individually by cohort and 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.

9.4.4 Pharmacokinetic Analyses

Assessment of the plasma PK of AZD4573 as monotherapy and in combination with other module-defined anti-cancer agents when given in combination is a secondary objective for the study.

The endpoints for these analyses are plasma concentrations and derived PK parameters for AZD4573 summarised by cohort for the PK analysis set. Plasma/serum concentrations and derived PK parameters for other anti-cancer agents may be summarised by cohort for the PK analysis set, as applicable.

For details on PK analyses, please refer to the separate Bioanalytical Report.

9.4.5 Pharmacodynamics CCI Analyses

Assessment of pharmacodynamics CCI analyses are exploratory objectives for this study.

For details on pharmacodynamic analyses CCI analyses refer the relevant module.

9.5 Interim Analyses

See relevant module for information on planned interim analyses.

9.6 Data Monitoring Committee

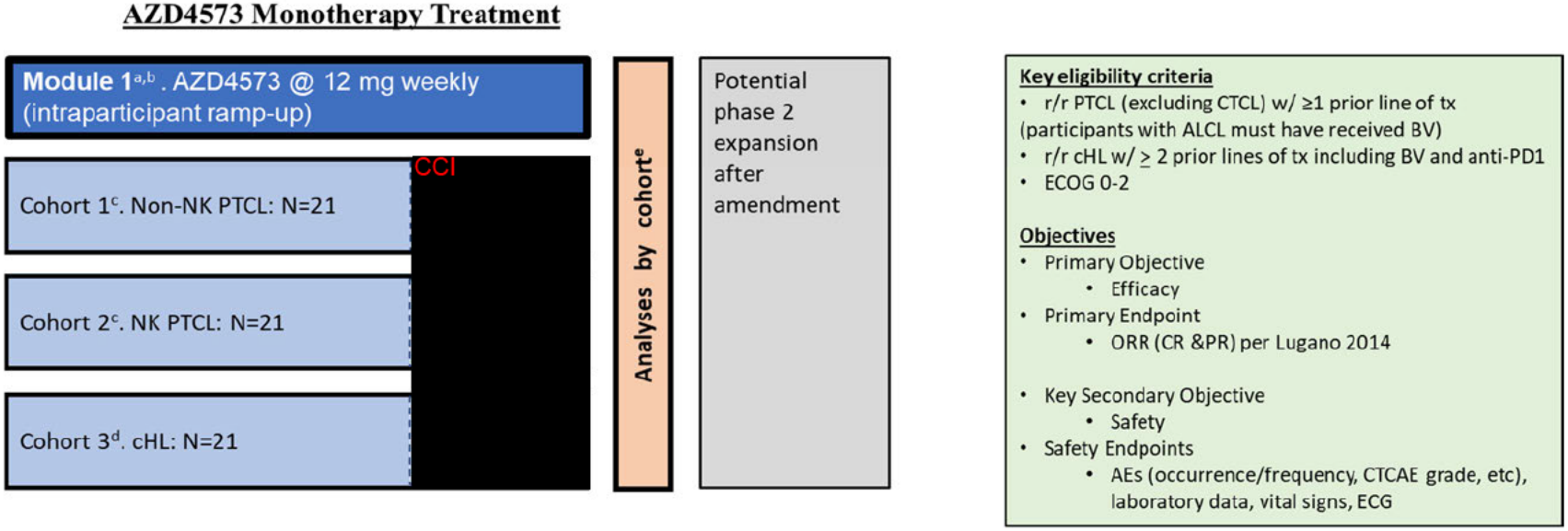
There will be no formal data monitoring committee for this study. See relevant module for information regarding the use of a SRC for this study.

10 MODULE 1

10.1 Summary – Module 1

10.1.1 Schema

Figure 5 Module 1 Schema: AZD4573 Monotherapy in Participants with r/r PTCL and r/r HL



[a] Dosing regimen based on AZD4573 monotherapy RP2D in lymphoma = 12 mg weekly.
[b] Dose confirmation in first 6 participants/cohort (safety/PK/PD) → SRC. Additional dose levels may be explored depending on the emerging clinical data in PTCL/cHL.
[c] Twenty-one participants per cohort, and CCI [redacted]
[d] Twenty-one participants per cohort, and CCI [redacted]
[e] Primary analysis at N = 21 for each cohort, with the primary analysis after approximately 6 months or when 75% of participants have progressed or died (Section 10.6). Additional data cuts may also be performed if required.

Abbreviations: AE, adverse event; ALCL, anaplastic large cell lymphoma; BV, brentuximab vedotin; cHL, classical Hodgkin Lymphoma; CR, complete response, CTCAE, Common Terminology Criteria for Adverse Events; CTCL, cutaneous T-cell lymphoma; DCO, data cut-off; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; N, number; NK PTCL, natural killer/peripheral T-cell lymphoma; ORR, overall response rate; PD, pharmacodynamic; PR, partial response; PTCL, peripheral T-cell lymphoma; r/r, relapsed/refractory; RP2D, recommended phase II dose.

10.1.2 Schedule of Activities

Table 9 Schedule of Activities: Module 1 (AZD4573 Monotherapy)

Procedure	Screening[a]	Cycle 1, Weeks 1-5 (includes intra-participant Dose ramp-up)	Cycle 2 to 12 (Cycle = 21 Days)			Cycles 13+ (Cycle = 21 days)	Disease Assessment	30-Day FU[e]	LTFU	Details in Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(± 2 Days)	(± 2 Days)			(± 7 Days)	(± 7 Days)	(± 7 Days)		
Informed consent[b]	X									Appendix A
Inclusion/exclusion	X									5 and 10.4.3
Medical history and demographics	X									5 and 10.4.3
Physical examination	X	X	X	X	X	X		X		10.8.2.1
ECOG performance status	X	X	X	X	X	X		X		10.8.2.1
B symptoms	X	X	X	X	X	X		X		10.8.2.2
Vital signs and weight	X	X	X	X	X	X		X		10.8.2.3
12-lead ECG	X	Refer to Section 10.8.2.4 for schedule						X		10.8.2.4
ECHO/MUGA	X	As clinically indicated						X		10.8.2.4
Cardiac troponin	X	X	X			X		X		10.8.2.5
T4, Cortisol, ACTH and TSH	X							X		10.8.2.5
EBV	Prior to receiving study treatment									10.8.9.2

Table 9 Schedule of Activities: Module 1 (AZD4573 Monotherapy)

Procedure	Screening[a]	Cycle 1, Weeks 1-5 (includes intra-participant Dose ramp-up)	Cycle 2 to 12 (Cycle = 21 Days)			Cycles 13+ (Cycle = 21 days)	Disease Assessment	30-Day FU[e]	LTFU	Details in Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(± 2 Days)	(± 2 Days)			(± 7 Days)	(± 7 Days)	(± 7 Days)		
Haematology[c]	X	X	X	X	X	X		X		10.8.2.5
Coagulation	X	X	X	X	X	X		X		10.8.2.5
Clinical chemistry[c]	X	X	X	X	X	X		X		10.8.2.5
Urinalysis	X	X	X			X		X		10.8.2.5
TLS monitoring (for at least 24 hours post SOI)	X	X								10.6.2.1.2
Pregnancy testing (WOCBP)	X	Pre-dose Week 1, Day 1	Prior to initiating a new cycle (once every 21 days)					X		10.8.2.5
Lipase/amylase	X	X	X	X	X	X		X		10.8.2.5
Hepatitis serology	X									10.8.2.5
Liver chemistry tests	X									10.8.2.5
Whole blood samples for CCI	X	Per Section 10.8.8.4					X	X		10.8.8.4
CCI sample for CCI	Prior to receiving study treatment									10.8.9.4

Table 9 Schedule of Activities: Module 1 (AZD4573 Monotherapy)

Procedure	Screening[a]	Cycle 1, Weeks 1-5 (includes intra-participant Dose ramp-up)	Cycle 2 to 12 (Cycle = 21 Days)			Cycles 13+ (Cycle = 21 days)	Disease Assessment	30-Day FU[e]	LTFU	Details in Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(± 2 Days)	(± 2 Days)			(± 7 Days)	(± 7 Days)	(± 7 Days)		
Serum immunoglobulins (IgA, IgM, IgG)	X		Day 1 of Cycles 3, 6 and 9 (pre-dose)			Cycle 13 (± 7 days) and every 6 months thereafter		X		10.8.2.6
Concomitant medication	X	X	X	X	X	X		X	X	5.2, 6.5
Adverse event evaluation		X	X	X	X	X		X	X	8.3
AZD4573 plasma PK		Refer to Section 10.8.6 for schedule								10.8.6
CCI		X								10.8.6
Pharmacodynamic samples (blood) for AZD4573		Weeks 1 to 3								10.8.7
CCI	X	Weeks 1 to 3	If elevated liver chemistry tests/bilirubin							10.8.9.3
Exploratory analyses samples	X	Refer to Section 10.8.8 for schedule								10.8.8

Table 9 Schedule of Activities: Module 1 (AZD4573 Monotherapy)

Procedure	**Screening[a]**	**Cycle 1, Weeks 1-5 (includes intra-participant Dose ramp-up)**	**Cycle 2 to 12 (Cycle = 21 Days)**			**Cycles 13+ (Cycle = 21 days)**	**Disease Assessment**	**30-Day FU[e]**	**LTFU**	**Details in Section**
		Cycle 1 Weeks 1-5, Day 1 Visits	**Days**			**Day**				
			1	**8**	**15**	**1**				
		(± 2 Days)	**(± 2 Days)**			**(± 7 Days)**	**(± 7 Days)**	**(± 7 Days)**		
Genomics Initiative sample (**optional**)		X								8.7
Bone marrow biopsy & aspirate (PTCL only)[d]	X						As clinically indicated and to confirm CR			10.8.9.1.1
Fresh or archival tumour tissue sample	X									10.8.9.1.2
Additional tumour biopsy sample (**optional**)							At disease progression	(X)		10.8.9.1.2
Disease assessments/radiologic scans	X		After Cycle 2 (+/- 1 week), then Q9W until W26 (Cycle 8, Week 3), then Q12W (+/- 1 week)					X		10.8.1
AZD4573 (IV; once weekly)[c]		X	X	X	X	X				10.6
Disease progression follow-up (SoC)									X	8.2.2

Table 9 Schedule of Activities: Module 1 (AZD4573 Monotherapy)

Procedure	Screening[a]	Cycle 1, Weeks 1-5 (includes intra-participant Dose ramp-up)	Cycle 2 to 12 (Cycle = 21 Days)			Cycles 13+ (Cycle = 21 days)	Disease Assessment	30-Day FU[e]	LTFU	Details in Section
		Cycle 1 Weeks 1-5, Day 1 Visits	Days			Day				
			1	8	15	1				
		(± 2 Days)	(± 2 Days)			(± 7 Days)	(± 7 Days)	(± 7 Days)		
Survival FU[e]									X	8.2.3

[a] Screening tests should be performed within 30 days before the first administration of study drug, unless otherwise indicated.
[b] Informed consent must be obtained ≤ 30 days before first dose of study drug and must be obtained before any protocol-defined screening tests are done.
[c] 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. To initiate Cycle 1 and subsequent cycles, haematology and chemistry criteria in inclusion criteria 10, 13, and 14 shall be met. In addition, during AZD4573 treatment, dose modification and discontinuation guidelines are provided in Section 10.6.1.
[d] Mandatory exploratory CCI analysis will be performed any time a bone marrow analysis is performed.
[e] The follow-up visit will be performed 30 days (± 7 days) after the last dose of all study drug. Disease assessments will be repeated at this visit if they have not been performed within 9 weeks if the participant discontinued before Week 26, or 12 weeks if the participant discontinued after Week 26.

Abbreviations: ACTH, adrenocorticotropic hormone; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; FU, follow-up; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IV, intravenous; LTFU, long-term follow-up; MUGA, multigated acquisition; PK, pharmacokinetic; PTCL, peripheral T-cell lymphoma; SoC, standard of care; SOI, start of infusion; TLS, tumour lysis syndrome; TSH, thyroid stimulating hormone; WOCBP, women of childbearing potential.

10.2 Introduction – Module 1

Module 1 of this study will evaluate the efficacy, safety, and tolerability of AZD4573 monotherapy in participants with r/r PTCL or r/r cHL. For an overview of the study design see Figure 5.

10.3 Objectives and Endpoints – Module 1

Type	Objectives	Endpoints
Primary		
Efficacy	To assess the efficacy of AZD4573 by evaluation of objective response rate.	• Endpoint based on Lugano response criteria for malignant lymphoma (Cheson et al 2014): – ORR, defined as the proportion of participants who have a tumour response (CR and PR)[a]
Secondary		
Efficacy	To assess efficacy of AZD4573 by evaluation of tumour response and OS.	• Endpoints based on Lugano response criteria for malignant lymphoma (Cheson et al 2014): – CR rate – DoR – PFS • OS
Safety	To assess the safety and tolerability of AZD4573.	Adverse events, laboratory data, vital signs, and ECG changes. Assessments related to AEs cover: • Occurrence/frequency • Relationship to IP as assessed by investigator • CTCAE grade • SAEs • Death • AEs leading to discontinuation of IP • AEs leading to dose modifications • AESIs

PK	To assess the plasma PK of AZD4573.	• Plasma concentrations and derived PK parameters for AZD4573
Exploratory		
PD	To assess the pharmacodynamics of AZD4573.	• CCI
CCI	CCI	• CCI
CCI	CCI	• CCI
Genetics	To collect and store CCI a CCI sample, for future exploratory research CCI	• CCI

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

Abbreviations: AE, adverse event; CCI; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DoR, duration of response; ECG, electrocardiogram; IP, investigational product; CCI 1; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; CCI; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; CCI; SAE, serious adverse event; TTR, time to response.

10.4 Study Design – Module 1

This is a modular, Phase II, multicentre, open-label dose confirmation and expansion study. Module 1 will assess the efficacy of AZD4573 as a monotherapy in r/r PTCL and r/r cHL populations. For an overview of the study design see Figure 5.

- AZD4573 will be administered intravenously as a monotherapy to participants with r/r PTCL or r/r cHL, including an intra-participant dose ramp-up. For dose regimen, see Section 10.4.1 below.
- For details on study design applying to all modules, including information on the SRC and the definitions for end of study, refer to the core protocol study design (Section 4.4).

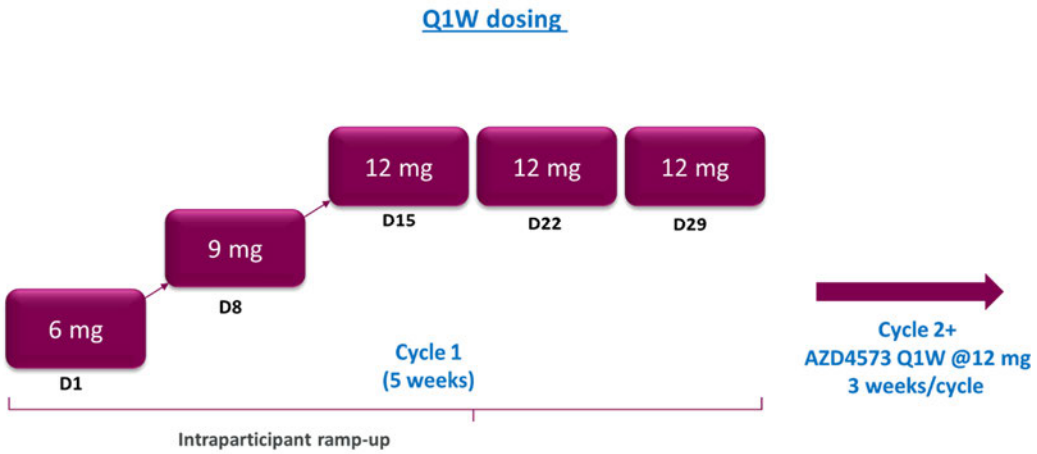
10.4.1 Module 1 Design: AZD4573 monotherapy

Module 1 is non-randomised and will consist of 2 r/r PTCL cohorts and 1 r/r cHL cohort; see Figure 5 and Table 10 below for planned participant numbers.

Each cohort will include an intra-participant dose ramp-up, starting at 6 mg AZD4573 (Figure 6). The target dose following the ramp-up is 12 mg attained on Week 3 of Cycle 1. During the first cycle, participants will receive a single dose of AZD4573 once weekly beginning with 6 mg Week 1, 9 mg Week 2, and 12 mg for each of Weeks 3 to 5.

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

Figure 6 Module 1 AZD4573 Monotherapy Dosing Regimen in PTCL and cHL including Intra-Participant Dose Ramp-Up



Abbreviations: cHL, classical Hodgkin Lymphoma; D, day; PTCL, peripheral T-cell lymphoma; Q1W, once weekly.

A comprehensive initial review of all safety and PK/PD data will be conducted in approximately the first 6 participants of each cohort (safety run-in), with separate SRCs for each cohort executed independently. The safety assessment will be undertaken by the SRC and is detailed in Section 10.4.4. The study procedures and safety assessments undertaken for the first cycle will be as per the SoA (Table 9). Each cohort will have a separate dose confirmation, assessed independently by the SRC, to assess safety and PK/PD data compared to the known profiles in the first time in human study (Study D8230C00001) lymphoma population.

These SRC reviews will confirm whether the RP2D for lymphoma (IV infusion 12 mg once weekly, including intra-participant ramp-up) is safe and tolerable or if additional dose optimisation is indicated at a revised dose and/or schedule. All cohorts can be opened and delivered independently of each other.

The role and responsibilities of SRC members, as well as the purpose and timing of the SRC meetings are described in the SRC Charter.

In addition to the initial safety run-in evaluation conducted separately within each cohort, pooled safety monitoring will be conducted every three months after the initial 15 dosed patients, pooled across the three cohorts, have had an opportunity to be treated for at least 8 weeks. If > 25% of participants experience any AEs related to study intervention that result in discontinuation of study treatment, the study data will be evaluated by the SRC. Enrolment may be paused until the safety data review by the SRC has been completed.

Other criteria for stopping or pausing the recruitment are described in Section 7.1.1.

CCI [redacted]

If 1 or more cohorts show a favourable safety and efficacy profile by the primary analysis then further expansion cohorts may be added via a protocol amendment. The DCO for the primary analysis for each cohort will occur after all response-evaluable participants in the cohort have had the opportunity to be followed for at least 6 months since their first dose or have progressed or have initiated other anticancer therapy, or when 75% of participants have progressed or died, whichever occurs first. Additional data cuts may also be performed if required.

Table 10 Module 1: Planned Response-Evaluable Participant Population

Cohort	Population	Number of participants[a]	Line of therapy
Cohort 1	PTCL, all comers (excluding NKTCL)	21	2+
Cohort 2	PTCL (NKTCL only)	21	2+
Cohort 3	cHL	21	3+

[a] CCI [redacted]

Abbreviations: cHL, classical Hodgkin Lymphoma; NKTCL, natural killer/T-cell lymphoma; CCI [redacted]; PTCL, peripheral T-cell lymphoma.

10.4.2 Justification for Dose

The planned starting and target doses of AZD4573 for Module 1 are as per the RP2D already determined for lymphoma in the ongoing Phase I monotherapy study of AZD4573 (D8230C00001).

CCI 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 and academic 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.

CCI

Furthermore, exploratory data from CCI samples collected from ongoing Phase I monotherapy study support target engagement CCI at all doses tested to date (ie, 6 mg and above), with a median CCI of CCI (range: CCI CCI) observed following the 12 mg weekly regimen (based on preliminary PK/PD modelling). Corresponding biological effects, eg, CCI CCI have also been observed.

In addition, based on exposure versus safety analysis conducted for the Phase I monotherapy

study, [redacted]

Overall, these analyses support the evaluation of AZD4573 12 mg, once weekly, monotherapy regimen in the treatment of patients with r/r PTCL or r/r cHL.

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

10.4.3 End of Module Definition

Refer to Section 4.4 in the core protocol for the 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.

All participants will continue to be followed for survival after objective disease progression until death, lost to follow-up, AstraZeneca closes the Module, or withdrawal of consent, whichever occurs first, up to the final analysis DCO.

Any participants still receiving study intervention at the completion of the final analysis will be able to continue to receive the intervention at the sponsor's discretion for up to 2 years, if the participant is still considered to be deriving clinical benefit and the sponsor is continuing development of the IP. Such participants will continue to be monitored for all SAEs up to 30 days after the last dose of the intervention therapy. Participants who continue to demonstrate clinical benefit after this 2 year treatment period will be eligible to receive AZD4573 as monotherapy or as part of a combination therapy via a rollover study requiring approval by the responsible Health Authority and ethics committee or through another mechanism at the discretion of the sponsor.

10.4.4 Safety Review Committee

A study-specific SRC will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety, PK, and other relevant data.

The SRC will be responsible for making recommendations for dose confirmation or modification All participants will be followed for safety through the entire duration of treatment.

A comprehensive initial review of all safety data will be conducted in approximately the first 6 participants of each cohort (safety run-in), with separate SRCs for each cohort executed independently. Recruitment will not be paused during this review. These participants will be

followed until all have completed Cycle 1, to ensure the treatment schedule is safe and tolerable. The SRC will review the totality of all relevant data (eg clinical, laboratory, safety) prior to providing decisions on study conduct. All decisions by this committee will be documented and shared in writing with all participating sites.

If, on an ongoing basis, > 25% of participants experience any AEs related to study intervention that result in discontinuation of study treatment, study data will be evaluated by the SRC. Enrolment may be paused until the safety data review by the SRC has been completed. Following this SRC review, additional monitoring may be implemented and/or enrolment and dosing may resume at a lower dose level or on a modified schedule. The SRC will meet at least every 6 months to review the overall safety and clinical data from the study.

At any time point 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 study drug interruption and a comprehensive review of safety.

10.5 Study Population – Module 1

Refer to Section 5.1 and Section 5.2 in core protocol for inclusion and exclusion criteria, respectively.

10.6 Study Intervention – Module 1

AZD4573 is administered as an absolute (flat) dose, 2-hour (± 15 minutes) intravenous infusion on a once weekly schedule. CCI [redacted]

Arm name	N/A
Intervention name	AZD4573
Type	Drug
Dose formulation	Concentrate for solution for infusion
Unit dose strength(s)	1.5 mg/ml
Dosage level(s)	6 mg AZD4573 (starting dose) 9 mg AZD4573 12 mg AZD4573 (target dose)
Route of administration	IV infusion
Use	Experimental
IP or NIP	IP
Sourcing	Provided centrally by the sponsor
Packaging and labelling	Study Intervention will be provided in a clear glass vial. Each vial will be labelled as required per country requirement.
Former names	AZ13810325

IP, investigational product; IV, intravenous; NIP, non-investigational product.

10.6.1 Dose Modification

Dose modification and discontinuation guidelines for haematological and non-haematological toxicities (excluding abnormal liver chemistry test results) are shown below in Table 11. Dose modifications for AZD4573 for abnormal liver chemistry test results are described in Table 12.

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 11 for recommended dose modifications for AZD4573) and supportive therapy administered as required. If the toxicity resolves or reverts in line with the dose modification guidelines below and the participant was showing clinical benefit, treatment with study treatment(s) may be restarted.

If the toxicity does not resolve in line with the dose modification guidelines below, then the participant should be discontinued from the study treatment and observed until resolution of the toxicity. Maximal drug interruption allowed for AZD4573 is 21 consecutive days; 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 Study Physician.

Table 11 Recommended Dose Modifications for AZD4573

Event[a]	Occurrence	Action with AZD4573
Tumour Lysis Syndrome (TLS)		
Changes in uric acid, potassium, phosphorus, creatinine or calcium, or symptoms suggestive of TLS	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.
		For events of Howard Grade 1 or 2 TLS, resume at same dose level upon resolution.
		For **first occurrence** of Howard Grade 3 TLS resume at the same dose upon resolution to Grade 1.
		For **second occurrence** of Howard Grade 3 TLS, after resolution to Grade 1, reduce dose by 1 dose level when re-starting AZD4573 except events that in the opinion of the investigator, in consultation with the Study Physician, are not dose limiting. For **subsequent occurrences** of Howard Grade 3 TLS, further re-challenge and dose level to be discussed with the Study Physician. For events of Howard Grade 4 TLS, discontinue AZD4573.
Non-haematological toxicities (except liver dysfunction and TLS)		

Event[a]	Occurrence	Action with AZD4573
Grade 3 or 4 non-haematological toxicities	First 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. After resolution of Grade 3 event to Grade 1, AZD4573 therapy may be resumed at the same dose. No dose modification is required. After resolution of Grade 4 event to Grade 1, reduce dose by one dose level when re-starting AZD4573.
	Second occurrence	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 re-starting AZD4573. If no resolution within 21 days discontinue AZD4573[b].
	Third occurrence	Discontinue AZD4573.
Haematological Toxicities		
Grade 3 or 4 neutropenia without fever or infection, lasting > 7 days despite growth factor support	First occurrence	Withhold dosing AZD4573 until Grade ≤ 2 or baseline level. Restart at same dose level following resolution.
	Second and subsequent occurrences	Withhold dosing AZD4573 until Grade ≤ 2 or baseline level. Restart with 1 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 Study Physician.
Grade 3 or 4 neutropenia with infection or fever	First 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.
	Second 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 1 dose level.

Event[a]	Occurrence	Action with AZD4573
	Third occurrence	Discontinue AZD4573.
Grade 3 thrombocytopenia without bleeding	Any	Withhold AZD4573 until Grade ≤ 2 or baseline level. Restart AZD4573 at the same dose level.
Grade 4 thrombocytopenia without bleeding requiring blood or platelet transfusion	First occurrence	Withhold AZD4573 until Grade ≤ 2 or baseline level. Restart AZD4573 at the same dose level.
	Second 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.
	Third occurrence	Discontinue AZD4573.
Grade 3 or 4 thrombocytopenia with bleeding requiring blood or platelet transfusion	First 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.
	Second occurrence	Discontinue AZD4573.

[a] Adverse reactions are graded using NCI CTCAE version 5.0.
[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 Study Physician.
Abbreviations: ANC, absolute neutrophil count; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; G-CSF, granulocyte-colony stimulating factor.

Dose modifications for AZD4573 for abnormal liver chemistry test results are described in Table 12.

Table 12 Recommended Dose Modifications for AZD4573 for Abnormal Liver Chemistry Test Results

Event[a]	Action
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.

Event[a]	Action
Grade 2 Isolated ALT/AST > 3 to ≤ 5 × ULN or Isolated Bilirubin > 1.5 to ≤ 3 × ULN	After 7 days if hepatic enzymes resolve to Grade ≤ 1, re-challenge at same dose level.
Grade 3 Isolated ALT/AST > 5 to 20 × ULN	If recovered to Grade ≤ 1 within 7 days, allow re-challenge at same dose level. If not recovered to baseline level within 7 days, discontinue AZD4573.
Grade 3 Isolated Bilirubin > 3 to 10 × ULN	If recovered to baseline level within 96 hours (-2/+12 hours) of start of dose allow re-challenge at same dose level. If not, discontinue AZD4573.
Grade 4 Isolated ALT > 20 × ULN or Isolated Bilirubin > 10 × ULN	Discontinue AZD4573.
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.
Grade 4[c] Isolated AST elevation ≥ 20 × ULN without concomitant elevation in ALT ≥ 20 × ULN or TBL ≥ 2 × ULN	**First occurrence** If recovered to Grade ≤ 1 or baseline level within 7 days of start of dose allow re-challenge at same dose level.
	Second occurrence If recovered to Grade ≤ 1 or baseline level within 7 days of start of dose allow re-challenge with 1 dose level reduction.
	Third occurrence Discontinue AZD4573.
Concurrent elevations in ALT, AST, or bilirubin (Please also refer to the HL appendix in the CSP 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.

Event[a]	Action
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.
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.
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.
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, re-challenge at same dose level[c].

[a] Adverse reactions are graded using NCI CTCAE version 5.0.
[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 re-challenge 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.
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; HL, Hy's Law; INR, international normalised ratio; PHL, Potential Hy's Law; TBL, total bilirubin; ULN, upper limit of normal.

10.6.2 Prevention and Toxicity Management of Risks for AZD4573 Monotherapy

This section provides recommendations for treatment of potential toxicities associated with AZD4573, and guidance about modifying the dose of AZD4573 due to those toxicities. For complete safety information refer to the IB for AZD4573.

Generally, Grade 1 or 2 non-haematological and/or haematological toxicities do not require AZD4573 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. These are described in Table 11 and Table 12 in the Section 10.6.1 (Dose Modification – Module 1).

10.6.2.1 Tumour Lysis Syndrome (TLS)

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

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. Prevention and management of TLS is dependent on risk stratification, and risk-based prophylaxis and management (Howard et al 2016). Participants identified with TLS potential per published risk guidelines (Coiffier et al 2008; Table 13) should be provided with adequate hydration, pharmacological pretreatment with allopurinol or rasburicase, and be carefully monitored for development of TLS. The risk of TLS associated with AZD4573 is anticipated to be lower for participants with PTCL or cHL compared to participants with DLBCL, as TLS is less often seen in these populations (Gopal et al 2015; Chen et al 2017; Coiffier et al 2014; O'Connor et al 2015; O'Connor et al 2011) .

The Howard modification of the Cairo-Bishop definitions of clinical and laboratory TLS are included in Appendix G. Laboratory or clinical TLS may trigger dose modification in accordance with guidelines provided in Table 11.

10.6.2.1.1 TLS Prophylaxis

Tumour lysis syndrome (TLS) prophylaxis is mandatory for **all** participants starting 3 days before the first dose of AZD4573. TLS prophylaxis is mandatory for all infusions as outlined below in Table 13 which provides TLS prophylaxis guidance, which 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 Study Physician.

In addition to the criteria outlined in Table 13 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 and IV fluid is permitted at any time during screening and treatment, however rasburicase and allopurinol must not be co-administered (Jones et al 2015).

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 ramp-up, SoC therapy 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.

Table 13 Mandatory TLS Prophylaxis Guidance (in Addition to Institutional Guidance)

Intermediate to High Risk	
LDH > ULN OR any lymph node ≥ 5 cm	
Prophylaxis	
Hydration[a]	Oral (1.5-2 L/day) plus additional IV fluid: Normal saline 500 mL over 2 to 4 hours prior to AZD4573, then 100 to 175 mL/h as tolerated to maintain urine output.
Antihyperuricemics	Allopurinol 300 mg orally twice daily beginning 3 days prior to AZD4573 and continuing at least through the end of Week 1b. Consider prophylactic rasburicasec if baseline uric acid is elevated above ULNd, LDH > 2 × ULN, or high tumour burden.

[a] Administer more aggressive IV fluid hydration for any participant who cannot tolerate or maintain oral hydration.
[b] After the end of Week 1, or upon discussion and agreement with the Study Physician, the dose or frequency of allopurinol may be reduced. Note: The dose of allopurinol should be reduced for renal insufficiency.
[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.
Adequate supportive therapy as per Institutional guidelines should be given for all toxicities.
NOTE: TLS prophylaxis/management with rasburicase and IV fluid is permitted at any time during screening and treatment. Rasburicase and allopurinol must not be co-administered.
Abbreviations: h, hour; IV, intravenous; LDH, serum lactate dehydrogenase; ULN, upper limit of normal.
Modified from Coiffier et al 2008.

10.6.2.1.2 TLS Monitoring and Management

Please refer to Appendix G for the definition of TLS and the TLS grading criteria to be used in this study.

All participants will receive TLS prophylaxis during the intra-participant dose ramp-up and be monitored for TLS during the first 24 hours post start of infusion during the intra-participant dose ramp-up (see Sections 10.6.2.1.1 and 10.6.2.1.2). If there are no signs of TLS at the 6 hour TLS monitoring assessment, the participant can be managed as an outpatient at the discretion of the investigator and return to the clinic the next day to complete the 24 hour TLS monitoring assessment. Participants showing signs of TLS at 6 hours after the start of infusion must remain admitted for inpatient TLS monitoring approximately every 6 hours (or more frequently if clinically indicated) until the 24 hour TLS monitoring assessment.

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

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. For each TLS monitoring timepoint, a TLS Monitoring page in the eCRF is to be filled out.

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, prophylaxis should be administered prior to AZD4573 per Section 10.6.2.1.1 and repeated as clinically indicated thereafter as per local standard.

Monitoring for TLS includes checking potassium, calcium, phosphate, uric acid, and creatinine. Fluid balance must be monitored according to institutional standards.

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.

10.6.2.1.3 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 (per Table 13), 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/hr as tolerated to maintain urine output at least until the 6 hour TLS monitoring lab assessment, and thereafter if medically indicated.

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.

10.6.2.2 Transaminases Increase With or Without Concomitant Bilirubin Increase and the Risk of Liver Injury

Transaminase elevations are an important identified risk for participants treated with AZD4573. Evidence of abnormal liver function 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 test results meet the criteria for expedited reporting.

Bilirubin increase with transaminase increase (ALT or AST or both) is included as an important identified risk for AZD4573. Biochemical changes of increased transaminases with concomitant increase in bilirubin fulfilling criteria for potential Hy's law have been observed in participants treated with AZD4573. These events resolved rapidly and have to date not been associated with any adverse clinical sequelae or lasting liver damage. Upon re-challenge with AZD4573, there is no consistent pattern of recurrence, nor is there any consistent increase in severity of the events. As such, whilst 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.

Liver injury is classified as an important potential risk for AZD4573. Participants who experience increases in transaminases or bilirubin levels after AZD4573 dosing must be monitored in line with Section 10.8.2.5. Please refer to Section 10.6.1 (dose modification and re-treatment) for additional information on how to manage a participant with increases in transaminases/bilirubin.

Additional CCI [redacted] will also be collected for central analysis (see Section 10.8.9.3).

If bilirubin fails to resolve within 96 (-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 Follow-up and LTFU visits), and the event must be immediately communicated to AstraZeneca.

For guidance on treating liver toxicity, please refer to Section 10.6.2, Table 12.

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.

Appendix E describes 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 Study Physician, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met.

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.

Available transcriptomic and clinical pathology data from the FIH study of AZD4573 monotherapy suggests 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 the 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 profiled from available FIH study clinical data as yet. Assessment of ALT changes from baseline versus cumulative dexamethasone dose suggests a possible trend towards a negative correlation, ie, high dexamethasone doses being associated with smaller increases in ALT post-baseline.

10.6.2.3 Diarrhoea

Diarrhoea is an important identified risk for AZD4573, based on monkey preclinical toxicology studies and clinical data accumulated to date.

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.

Prophylaxis for diarrhoea with atropine is strongly recommended for all participants enrolled into the study as an anticholinergic 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, 1 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 intravenous fluids.

10.6.2.4 Nausea and Vomiting

Nausea and/or vomiting are important identified risks for AZD4573. 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.

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 (e.g. 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 (eg, 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 8 mg dexamethasone 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.

10.6.2.5 Neutropenia and Febrile Neutropenia

Neutropenia and febrile neutropenia are important identified risks for participants treated with AZD4573. In the presence of CTCAE Grade 3/4 neutropenia, 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. However, colony-stimulating factors including G-CSF or pegylated G-CSF has 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. Anti-viral 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 guidelines and International National Comprehensive Cancer Network/European Society for Medical Oncology/American Society of Clinical Oncology guidelines.

10.6.2.6 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 toxicology studies. 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.

Common treatable causes of anaemia (e.g., 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.

10.6.2.7 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.

10.6.2.8 Drug-Drug Interactions

Drug-drug interactions is a potential risk for AZD4573 and refers to interactions with potent CYP3A4 inhibitors. Specific drug-drug interaction studies have not yet been performed for AZD4573.

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. However, clinical studies have not yet been performed to access the 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.

10.6.2.9 Myocardial Ischaemia and Heart Rate Increase

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 measurements for all participants as described in Section 10.8.2. ECG and troponin measurements must be performed for all participants who develop symptoms suggestive of myocardial ischaemia.

10.6.3 Criteria for Restarting Treatment

The criteria to be met before a participant receives further study drug infusions following a pause in treatment, either within 1 cycle or between cycles, is as below:

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 > 75000/μL or > 50000/μL with bone marrow involvement.

3 Participant has recovered from all hepatic toxicity events within the timeframes described in Table 12 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 5 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 11.

10.7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal – Module 1

See the SoA (Section 10.1.2) for data to be collected at the time of intervention discontinuation and follow-up and any further evaluations that need to be completed.

Please refer to Section 7 (Core protocol) for information on discontinuation of study intervention and participant discontinuation/withdrawal.

10.8 Study Assessments and Procedures – Module 1

- Study procedures and their timing are summarised or linked to in the SoA. 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 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 maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, is not anticipated to exceed 436.5 mL in Cycle 1 (cycle duration of 5 weeks) and 124 mL in each subsequent cycle (cycle duration of 3 weeks).

10.8.1 Efficacy Assessments

10.8.1.1 Disease Assessment Criteria

Disease assessments for PTCL and HL will be done by the investigator using the Lugano Response Criteria (Cheson et al 2014).

Table 14 The Lugano Response Criteria

Response and Site	PET-CT-Based Response	CT-Based Response
Complete:	**Complete metabolic response:**	**Complete radiologic response (all of the following):**
Lymph nodes and extra-lymphatic sites	Score 1, 2, 3[a] with or without a residual mass on 5PS[b] It is recognised that in Waldeyer's ring or extra-nodal sites with 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 extra-lymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement[c]	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 extra-lymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extra-nodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured 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

Table 14 The Lugano Response Criteria

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, extra-nodal lesions	Score 4 or 5[b] 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 extra-nodal sites; no criteria for progressive disease are met
Non-measured 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 Extra-nodal lesions	Score 4 or 5[b] with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	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 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

Table 14 The Lugano Response Criteria

Response and Site	PET-CT-Based Response	CT-Based Response
Non-measured lesions	None	New or clear progression of pre-existing non-measured 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 extra-nodal 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] A score 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 extra-nodal 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, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured 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 extra-nodal 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 extra-nodal 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 or myeloid growth factors).

[b] 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; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter; MRI, magnetic resonance imaging; PET, positron-emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.
Cheson et al 2014

10.8.1.2 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 15

below, and thereafter to confirm CR or as clinically indicated. Unscheduled radiologic scans may be performed at investigator discretion if deemed clinically indicated.

Table 15 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 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.

10.8.2 Safety Assessments

Planned time points for all safety assessments are provided in the Module 1 SoA (Section 10.1.2) and are detailed below.

10.8.2.1 Physical Examinations

Baseline/screening:

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 that may qualify as AEs.

Post first dose of AZD4573:

From the first dose of AZD4573 onwards, symptom-directed physical examinations will be performed before each infusion and at the 30-day follow-up visit as specified in the Module 1 SoA (Section 10.1.2).

ECOG performance status:

Performance status will be assessed at screening, before each dose of AZD4573 and at the 30-day follow-up according to ECOG criteria as follows:

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

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a

light or sedentary nature eg, light housework, office work.

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

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

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

10.8.2.2 B symptoms

Information on B symptoms (e.g., unintentional weight loss, fevers and night sweats) will be collected at each visit.

10.8.2.3 Vital Signs

Vital signs (body temperature, blood pressure [BP], heart [pulse] rate and body weight) will be performed at timelines specified below.

- Blood pressure and pulse/heart rate measurements will be assessed in supine position 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.
- Vital signs are to be taken before any blood collection.
- Body temperature will be taken prior to all infusions (within 2 hours before start of the infusion).
- Weight will be measured at screening, prior to infusions on Day 1 of each cycle, and at the 30-day follow-up visit.

Blood pressure and pulse rate will be measured at the following timepoints:

- Screening
- On Day 1 of each AZD4573 dose in Cycle 1
- Cycle 2 Day 1 at the following timepoints:
  - Pre-dose (up to 2 hours prior to infusion)
  - 1 hour after the start of the infusion (± 10 minutes)
  - At end of infusion (up to 10 minutes post-dose)
  - 4 hours (± 30 minutes) after end of infusion
  - 6 hours (± 30 minutes) after end of infusion

- For all subsequent infusions:
  - Pre-dose (up to 30 minutes prior to infusion)
  - At the end of infusion (up to 30 minutes post-dose)
- At the 30-day follow-up visit.

10.8.2.4 Electrocardiograms

ECG will be performed at timepoints specified below.

Twelve-lead digital ECGs will be obtained after the participant has been resting semi-supine for at least 10 minutes. 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 Study Physician.

Single ECGs will be collected for central analysis at the timepoints below:

- Screening
- During Cycle 1, all weeks:
  - Pre-dose (up to 2 hours prior to infusion)
  - End of infusion (within 30 minutes of the end of infusion)
- Cycle 2 Day 1
  - Pre-dose (up to 2 hours prior to infusion)
  - End of infusion (within 30 minutes of the end of infusion)
- Cycle 3+: End of infusion (within 30 minutes of the end of infusion)
- 30-day follow-up visit

The ECG parameters to be determined will include (but will not be limited to) the following:

- Heart rate
- RR interval: duration in msec between 2 R peaks of 2 consecutive QRS complexes
- PR interval: duration in msec from the beginning of wave P to onset of ventricular depolarisation (Q and R)
- QRS interval: duration in msec of the QRS complex
- QT interval: duration in msec from the beginning of Q wave to the end of the T-wave
- QTcF: QT interval corrected for heart rate using Fridericia's formula (QT[msec]/RR[sec]1/3)

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 eCRF form.

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 (see Section 10.8.2.5).

Echocardiograms: In addition to screening, an ECHO should be done within 14 days after an abnormal ECG finding (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.

10.8.2.5 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the timepoints indicated below.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

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. To initiate Cycle 1 and subsequent cycles, haematology and chemistry criteria in inclusion criteria 10, 13, and 14 shall be met.
In addition, during AZD4573 treatment, dose modification and discontinuation guidelines are provided in Section 10.6.1. For each TLS monitoring timepoint, a TLS Monitoring page in the eCRF is to be filled out. If clinically indicated, additional clinical laboratory tests and evaluations may be performed by the investigator and these need to be entered into the eCRF.

The laboratory variables to be measured for haematology/haemostasis, clinical chemistry, urinalysis, coagulation, and pregnancy testing are listed in Table 16.

- **Haematology:** should be measured at screening, during Cycles 1 to 3 before AZD4573 dosing and 24 hours post start of infusion, before dosing for Cycles 4+, and at the 30-day

follow-up. From Cycle 4 onwards, a 24-hour sample is only required where clinically indicated.

- **Clinical chemistry:** blood samples should be taken during Cycles 1 to 3 before AZD4573 dosing and 24 hours post start of infusion, before dosing for Cycles 4+, and at the 30-day follow-up. From Cycle 4 onwards, a 24-hour sample is only required where clinically indicated.
  - In addition, GLDH and CPK will be measured at screening for all participants. For any participant on study who experiences elevated ALT or AST ≥ 3 × ULN and/or total bilirubin ≥ 2 × ULN after dosing, repeated measurements of liver chemistry tests are required at least every 48 hours (-2/+12 hours) post start of infusion until resolution of the event to baseline level.
  - Note that additional samples are required for TLS monitoring at baseline and prior to infusion, 6 hours after start of infusion, and 24 hours after start of infusion during the intra-participant ramp-up; see TLS monitoring below for further 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.
- **Coagulation:** should be measured at screening, during Cycles 1 to 3 before AZD4573 dosing and 24 hours post start of infusion, before dosing for Cycles 4+, and at the 30-day follow-up. From Cycle 4 onwards, a 24-hour sample is only required where clinically indicated.
  - INR/PT and fibrinogen (and D-dimer where available at local institution) should be measured at 96 (-2/+12) hours and 7 days post start of infusion for any participant experiencing ALT or AST elevations ≥ 3 × ULN with concomitant elevation in total bilirubin ≥ 2 × ULN, then as clinically indicated until resolution of the liver chemistry test abnormality to baseline level.
- **Urinalysis:** should be done at screening, up to 30 minutes prior to infusion on Day 1 of each cycle, and at the 30-day follow-up.
- **Supra-renal glands:** T4, cortisol, adrenocorticotropic hormone and TSH should be measured at screening and at the 30-Day FU.
- **Pancreas:** Lipase and amylase measurements are required at screening, pre-dose on each AZD4573 dosing day, and at the 30-Day FU.
- **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 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.

- **Pregnancy:** a urine or serum sample for a pregnancy test will be collected from all female participants of childbearing potential at the following timepoints:
  - Screening
  - Pre-dose on Cycle 1, Day 1
  - Prior to initiating a new cycle (once every 21 days)
  - At the 30-day follow-up visit.

  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.
- **Cardiac:** Cardiac troponin measurements are required at:
  - Screening.
  - Cycle 1: pre-dose (up to 2 hours prior to infusion) and at 24 hours after start of infusion.
  - Cycle 2+: pre-dose (up to 2 hours prior to infusion).
  - 30-Day follow-up visit.
- **TLS monitoring**: potassium, calcium, phosphate, uric acid, and creatinine at baseline, then at the following timepoints for each infusion: prior to infusion, 6 hours after start of infusion, and 24 hours after start of infusion during the intra-participant ramp-up. Participants showing signs of laboratory TLS at 6 hours after infusion must be admitted for inpatient TLS monitoring for 24 hours and monitored every 4 to 6 hours during this time (or more frequently if clinically indicated); see Section 10.6.2.1.2.
- **Liver chemistry tests:** GLDH and CPK, will be measured at screening for all participants.

For any participant on study who experiences elevated ALT/AST (≥ 3 × ULN) and/or elevated total bilirubin (≥ 2 × ULN), repeated liver chemistry tests are required including: total and direct/indirect bilirubin, ALT, AST, ALP, C-reactive protein, CPK, GLDH, INR/PT, fibrinogen, D-dimer (where available at local institution). Liver chemistry tests should be measured at least every 48 hours (-2/+12 hours) post start of infusion until resolution of the event to baseline (or Grade 1) levels.

If liver chemistry tests are still elevated after 96 hours, then additional testing should be done with each subsequent chemistry panel test until resolution for each incidence of the elevated ALT and/or AST. During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator participates in review and assessment of these cases together with the sponsor. HL criteria are met if there is no alternative explanation for the elevations in transaminases and total bilirubin levels. If a participant is assessed as meeting PHL criteria, please refer to Appendix E ‘Actions required in cases of increases in liver

biochemistry and evaluation of HL', for further instructions.

The following laboratory variables for haematology/haemostasis, clinical chemistry, urinalysis, and pregnancy testing will be measured.

Table 16 Laboratory Safety Variables

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

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

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

10.8.2.6 Other Safety Assessments

Monitoring for TLS per the SoA (Section 10.1.2) and prophylaxis for TLS are outlined in detail in Section 10.6.2.1.2.

Blood samples for CCI [redacted] will be collected per the SoA (Section 10) and as outlined in Section 10.8.9.3.

Additional testing requirements (refer to the SoA [Section 10] for timing) include:

- Echocardiograms: In addition to screening, an ECHO should be done within 14 days after an abnormal ECG finding (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.
- Serum immunoglobulins (IgA, IgM, IgG): Screening, pre-dose on Day 1 of Cycles 3, 6, 9, 13, every 6 months thereafter and at the 30-Day FU.

10.8.3 Adverse Events and Serious Adverse Events

Refer to Section 8.3 in the core protocol.

10.8.4 Overdose

Refer to core protocol Section 8.4 for information on AZD4573 overdose.

10.8.5 Human Biological Samples

See core protocol Section 8.5 for detail on human biological samples.

10.8.6 Pharmacokinetics

Pharmacokinetics is a secondary objective for Module 1. Plasma samples will be used to analyse the PK of AZD4573 (and metabolites, if applicable). Samples collected for analyses of AZD4573 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

10.8.6.1 Pharmacokinetics Sampling Schedule

Plasma samples will be collected for measurement of plasma concentrations of AZD4573 at the following timepoints on Cycle 1, Day 1 of Weeks 1 through 3 and Cycle 2, Day 1:

- Pre-dose (up to 2 hours prior to AZD4573 administration)
- Following the start of infusion at the following timepoints:

- 1 hour (± 15 minutes)
- 2 hours (± 15 minutes)
- 4 hours (± 30 minutes)
- 7 hours (± 1 hour)
- 24 hours (± 1 hour) (ie, Cycle 1 Day 2).

Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

CCI
CCI

- CCI
- CCI
  - CCI
  - CCI
  - CCI

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

10.8.6.2 Determination of Drug Concentration

Samples for determination of drug concentration in plasma CCI will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Incurred sample reproducibility analysis, 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.

10.8.7 Pharmacodynamics

Whole blood samples will be collected and immediately processed (within 30 minutes) on-site for CCI. The objective of these studies is to evaluate whether AZD4573 is CCI CCI as expected, and to gain an understanding of kinetics and dose response. CCI CCI CCI

10.8.7.1 Collection of Samples

Mandatory pharmacodynamic (whole blood) samples will be collected at the following

timepoints:

- Screening
- Week 1 (6 mg AZD4573; starting dose)
  - C1D1 predose (up to 2 hours prior to dosing)
  - C1D1 2 hours (± 15 minutes) after start of infusion
  - C1D1 4 hours (± 30 minutes) after start of infusion
  - C1D1 7 hours (± 1 hour) after start of infusion
  - C1D2 24 hours (± 2 hours) after start of infusion
- Week 2 (9 mg AZD4573)
  - C1D8 predose (up to 2 hours prior to dosing)
  - C1D8 2 hours (± 15 minutes) after start of infusion
  - C1D8 4 hours (± 30 minutes) after start of infusion
  - C1D8 7 hours (± 1 hour) after start of infusion
  - C1D9 24 hours (± 2 hours) after start of infusion
- Week 3 (12 mg AZD4573; target dose)
  - C1D15 predose (up to 2 hours prior to dosing)
  - C1D15 2 hours (± 15 minutes) after start of infusion
  - C1D15 4 hours (± 30 minutes) after start of infusion
  - C1D15 7 hours (± 1 hour) after start of infusion
  - C1D16 24 hours (± 2 hours) after start of infusion

Note: The timing of these samples may be adjusted dependent upon ongoing PK and pharmacodynamic analysis and interpretation.

CCI must be collected at each pharmacodynamic timepoint once participants have reached the target dose.

Further details on sample processing, handling and shipment will be provided in the Laboratory Manual.

For storage, re-use and destruction of pharmacodynamic samples see Section 8.5 and Appendix C.

10.8.8 Exploratory Whole Blood Analyses Samples

Mandatory whole blood samples will be collected from all participants as per the schedule in Table 17 and the sections below.

Table 17 Exploratory Whole Blood Analyses Samples (All Participants)

Samples	Timepoints[a]																		
	Screening	C1D1		C1D2	C1D8		C1D9	C1D15		C1D16	C1D29	C2D1	C2D15	C3D1	C5D1	C6D1	C7D1	Tumour assessment scans[b]	EOT[c]
		pre	post	24h	pre	post	24h	pre	post	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		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 = up to 2 hours prior to dosing; post-dose = 2 hours (± 15 minutes) after start of infusion, and 24h = 24 hours (± 2 hours) 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.

[d] Exploratory CCI analysis.

[e] CCI analysis.

[f] CCI

[g] Samples in CCI tubes for CCI -based exploratory analysis.

[h] Samples in CCI tubes for CCI -based exploratory analysis.

Abbreviations: C1D1, Cycle 1 Day 1; CCI ; CCI ; EOT, end of treatment; CCI ; CCI ; post, post-dose; pre, pre-dose; 24h, 24 hours after infusion.

10.8.8.1 Whole blood for Exploratory [redacted] (all participants)

Mandatory whole blood samples to enable exploratory [redacted] analysis will be collected as specified below. Note: Collection time begins with the start of infusion.

- Screening
- C1D1 predose (up to 2 hours prior to dosing)
- C1D15 predose (up to 2 hours prior to dosing)
- C1D29 predose (up to 2 hours prior to dosing)
- C2D1 predose (up to 2 hours prior to dosing)
- C2D15 predose (up to 2 hours prior to dosing)
- C3D1 predose (up to 2 hours prior to dosing)
- C5D1 predose (up to 2 hours prior to dosing)
- C6D1 predose (up to 2 hours prior to dosing)
- C7D1 predose (up to 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

10.8.8.2 Whole Blood for [redacted] Analysis (All Participants)

Mandatory whole blood samples to isolate plasma for [redacted] and [redacted] analysis will be collected to [redacted] Note: Collection time begins with the start of infusion.

- Screening
- C1D1 predose (up to 2 hours prior to dosing)
- C1D15 predose (up to 2 hours prior to dosing)
- C1D29 predose (up to 2 hours prior to dosing)
- C2D1 predose (up to 2 hours prior to dosing)
- C2D15 predose (up to 2 hours prior to dosing)
- C3D1 predose (up to 2 hours prior to dosing)
- C5D1 predose (up to 2 hours prior to dosing)
- C6D1 predose (up to 2 hours prior to dosing)
- C7D1 predose (up to 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

10.8.8.3 Whole Blood Samples for [redacted] (All Participants)

Mandatory whole blood samples will be collected from all participants at the timepoints indicated below. [redacted] Note: Collection time begins with the start of infusion.

- Screening
- C1D1 predose (up to 2 hours prior to dosing)
- C1D15 predose (up to 2 hours prior to dosing)
- C1D16 24 hours (± 2 hours) after start of infusion
- C2D1 predose (up to 2 hours prior to dosing)
- C3D1 predose (up to 2 hours prior to dosing)
- C5D1 predose (up to 2 hours prior to dosing)
- C7D1 predose (up to 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

10.8.8.4 Whole Blood Samples for [redacted] (All Participants)

Mandatory whole blood samples will be collected from all participants at the timepoints indicated below. [redacted] Note: Collection time begins with the start of infusion.

- Screening
- C1D1 predose (up to 2 hours prior to dosing)
- C1D15 predose (up to 2 hours prior to dosing)
- C1D16 24 hours (± 2 hours) after start of infusion
- C2D1 predose (up to 2 hours prior to dosing)
- C3D1 predose (up to 2 hours prior to dosing)
- C5D1 predose (up to 2 hours prior to dosing)
- C7D1 predose (up to 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

10.8.8.5 Whole Blood for [redacted] Exploratory Analysis (All Participants)

Mandatory whole blood samples will be collected from all participants in [redacted] at the timepoints indicated below to [redacted] Note: Collection time begins with the start of infusion.

- Screening
- C1D1 predose (up to 2 hours prior to dosing)
- C2D1 predose (up to 2 hours prior to dosing)
- C3D1 predose (up to 2 hours prior to dosing)
- C5D1 predose (up to 2 hours prior to dosing)
- C7D1 predose (up to 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

10.8.8.6 Whole Blood for [redacted] Exploratory Analysis (All Participants)

Mandatory whole blood samples will be collected in [redacted] from all participants at the timepoints indicated below. [redacted] Note: Collection time begins with the start of infusion.

- Screening
- Week 1 (6 mg AZD4573; starting dose)
  - C1D1 predose (up to 2 hours prior to dosing)
  - C1D1 2 hours (± 15 minutes) after start of infusion
  - C1D2 24 hours (± 2 hours) after start of infusion
- Week 2 (9 mg AZD4573)
  - C1D8 predose (up to 2 hours prior to dosing)
  - C1D8 2 hours (± 15 minutes) after start of infusion

  - C1D9 24 hours (± 2 hours) after start of infusion
- Week 3 (12 mg AZD4573; target dose)
  - C1D15 predose (up to 2 hours prior to dosing)
  - C1D15 2 hours (± 15 minutes) after start of infusion
  - C1D16 24 hours (± 2 hours) after start of infusion
- C2D1 predose (up to 2 hours prior to dosing)
- C3D1 predose (up to 2 hours prior to dosing)
- C5D1 predose (up to 2 hours prior to dosing)
- C7D1 predose (up to 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

10.8.9 CCI [redacted]

10.8.9.1 Tissue Samples

10.8.9.1.1 Bone Marrow

All PTCL participants must be willing and able to provide mandatory baseline bone marrow aspirate and/or biopsy no older than 3 months, and agree to undergo post-treatment bone marrow biopsy when required to confirm response.

Where bone marrow biopsy is performed on a dosing day, it must be done at least 2 hours post-infusion.

For all participants, any time a bone marrow analysis is performed, mandatory exploratory CCI [redacted] analysis will be performed. CCI [redacted]

10.8.9.1.2 Tumour Tissue

Tumour tissue samples will be utilised to confirm cHL and PTCL histological subtype and for CCI [redacted]. The tumour biopsy samples may also be used as part of the CCI [redacted] assessments.

Fresh tumour tissue or archival tumour tissue must be confirmed to be available at screening. This should be provided as a fresh biopsy (preferable) where available and clinically feasible, or where a fresh biopsy is unavailable, an archival tumour biopsy sample FFPE tumour block may be provided. Where an archival tumour biopsy FFPE tumour block is unavailable,

archival tumour biopsy FFPE unstained slides must be provided.

For quantities, refer to the laboratory manual.

Archival tissues must have been obtained as a core biopsy or excisional node 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.

Where clinically feasible, participants may also consent to provide an additional **optional** biopsy at end of treatment/disease progression for analysis of candidate resistance mechanisms. Informed consent must be obtained from any participant who agrees to provide tissue for optional tumour tissue sample testing. This optional sample may be taken at the 30-day follow-up visit if not collected previously.

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 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.

Instructions on tumour biopsies processing, storage, and shipping will be provided in the Laboratory Manual.

10.8.9.2 Blood samples

EBV serology will be conducted at screening. EBV serology must include IgM and IgG. Any participants testing positive for EBV must also have EBV viral load (PCR) performed at screening. For participants with positive EBV serology at baseline, sites should enter historical EBV-encoded RNA in situ hybridisation and/or latent membrane protein 1 immunohistochemical data where available.

10.8.9.3 CCI [redacted]

Plasma samples will be collected from all participants to assess exploratory CCI [redacted]. These samples will be collected as per the timepoints in Table 18 below.

Table 18 CCI [redacted] Sampling Schedule (All Participants)

Day	Timing for blood samples	Window
Screening	At any screening visit	Not applicable
Cycle 1, Weeks 1-3	Predose	Within 2 hours before start of infusion
	4 hours post start of infusion	± 30 minutes
	7 hours post start of infusion	± 1 hour
	24 hours post start of Day 1 infusion	± 1 hour
In cases of increased liver chemistry tests/bilirubin at 24h post start of infusion	96 hours post start of infusion	-2/+12 hours
	Pre-dose the following infusion	Within 4 hours before start of infusion
	Each timepoint where chemistry panel testing is performed	N/A
Any visit from Cycle 1, Week 4 onwards where increased liver chemistry tests/bilirubin is observed (post dose chemistry panel test)	Same schedule as Cycle 1, Weeks 1-3	N/A

For all participants, plasma samples will be collected during Cycle 1, Weeks 1 to 3. In addition, if a participant has increases in liver chemistry tests/bilirubin (defined as any elevated transaminases of Grade 3 or above or fulfilling PHL criteria), samples should also be taken at 96 hours post start of infusion (-2/+12 hours), pre-dose the following infusion (within 4 hours) and whenever chemistry panel testing is being performed, until resolution of the event.

For any elevated liver chemistry tests/bilirubin that is observed with subsequent dosing with AZD4573, CCI [redacted] should be performed using the timepoints outlined above (excluding screening sample).

10.8.9.4 Other Study Related CCI [redacted] Research CCI [redacted] Sample for CCI [redacted]

Per local regulations, a mandatory CCI [redacted] sample for CCI [redacted] will be collected from participants in this module. It is important to assess CCI [redacted] will be used to discriminate this. The sample should be collected from participants before receiving study treatment.

Details on sample processing, handling, and shipment are provided in the Laboratory Manual. For storage, re-use and destruction of CCI samples see Section 8.5.

10.8.10 Optional Genomics Initiative Sample

See core protocol Section 8.7.

10.9 Statistical Considerations – Module 1

10.9.1 Statistical Hypotheses

Not applicable.

10.9.2 Sample Size Determination

Table 19 Sample Size: Module 1

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

CCI

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

Module 1 will include approximately 21 response-evaluable PTCL participants excluding NKTCL in Cohort 1, 21 response-evaluable NKTCL participants in Cohort 2, and 21 response-evaluable cHL participants in Cohort 3.

CCI This may enable the sponsor to continue enrolling participants, beyond the initial 21 response-evaluable per cohort, while considering further clinical development options based on an early suggestion of positive benefit-risk for participants with r/r PTCL treated with AZD4573 monotherapy.

CCI This may enable the sponsor to continue enrolling participants, beyond the initial

21 response-evaluable participants, while considering further clinical development options based on an early suggestion of positive benefit-risk for participants with r/r cHL treated with AZD4573 monotherapy.

CCI

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

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

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

Table 20 CCI

CCI

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 DCO for the primary analysis for each Module 1 PTCL cohort will occur after 21 response-evaluable participants in the cohort have had the opportunity to be followed for at

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

Historical response rates in r/r cHL 3L (excluding BV and anti-PD1) have been in the range of 10% to 50% (Vassilakopoulos et al 2020).

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

Table 21 CCI

CCI

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

In Module 1 cohorts a secondary objective is to confirm if the lymphoma RP2D is safe and tolerable or if additional dose optimisation at a revised dose is indicated. Up to a maximum of approximately 60 r/r PTCL participants and 30 r/r cHL participants will be treated with AZD4573 monotherapy in Module 1. The data from these approximately 90 new lymphoma participants would supplement safety data collected for participants treated at this dose level in D8230C00001. Module 1 will also provide further data for PK/PD modelling.

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

10.9.3 Populations for Analyses

For purposes of analysis, the study populations are defined as provided in Table 22. For the safety and PK analyses, participants will be classified according to the dose schedule they actually received. For all efficacy analyses, and for baseline and demography, participants will be classified according to the dose they were assigned to (ie, the planned dose schedule).

Table 22 Populations for Analyses

Population/Analysis set	Description
Enrolled	All participants who sign the ICF.
Safety	All participants who receive at least 1 dose of any study intervention.
Full analysis set/ITT	All participants who receive any amount of any study intervention. This is for efficacy, baseline and demography.
Response evaluable	All dosed participants who have measurable disease at baseline.
PK	All participants who receive any amount of study intervention with at least 1 reportable concentration.

Abbreviations: ICF, informed consent form; ITT, intention-to-treat; PK, pharmacokinetics.

10.9.4 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. Any deviations from this plan will be reported in the CSR.

10.9.4.1 General Considerations

Refer to Section 9.4.1 for core study details on statistical analyses.

The primary endpoint for Module 1 is ORR; other efficacy endpoints are secondary.

10.9.4.2 Efficacy Analyses

The efficacy endpoints of ORR, CR rate and DoR will be summarised on the response evaluable set. The efficacy endpoints of PFS and OS will be summarised on the full analysis set (ITT).

Additional subgroup analysis of efficacy may be performed as specified in the SAP.

The response criteria for malignant lymphoma (Cheson et al 2014) will be used, as assessed by investigators, to derive the endpoints (ORR, CR rate, DoR and PFS).

10.9.4.2.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is ORR, defined as the proportion of participants who have a

tumour response (CR and PR).

Overall Response Rate and Complete Response Rate

Overall response rate (and CR rate) will be presented with corresponding 80% and 95% 2-sided CIs.

10.9.4.2.2 Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints are CR rate, DoR, PFS and OS.

Duration of Response

Duration of response is defined as the time from the first objective response of CR or PR to the time of documented disease progression or death (in the absence of disease progression). It will be summarised using descriptive statistics and KM plots where there are sufficient numbers of responders.

Progression Free Survival

PFS is defined as the time from first dose date to documented disease progression, or death (by any cause in the absence of progression), regardless of whether the participant withdraws from study treatment 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 assessment.

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

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.

KM plots and estimates will be provided.

Overall Survival

Overall survival is defined as the time from first dose until the date of death from any cause. Any participant not known to have died by the analysis DCO date will be censored based on the last recorded date on which the participant was known to be alive. KM plots and estimates will be provided.

10.9.4.3 Safety Analyses

See core protocol Section 9.4.3 for safety analyses.

10.9.4.4 Pharmacokinetic Analyses

The secondary endpoints for PK are plasma concentrations and derived PK parameters for AZD4573. Additional details on PK analyses will be provided in the SAP.

10.9.4.5 Pharmacodynamics [redacted] analyses

Detail on exploratory endpoints will be contained in the SAP.

[redacted] status will be assessed for participants in each cohort according to pre-specified criteria that may be detailed in the SAP. [redacted] assessments may include, but are not limited to, pharmacodynamic analysis of [redacted] exploratory analyses may be described in a separate analysis plan and may be reported outside the CSR in a separate report or publication. The results of this [redacted] assessment may be pooled with [redacted] data from other studies with the study intervention to generate hypotheses to be tested in future research.

10.9.5 Interim Analyses

No interim analyses are planned for this module.

11 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 Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study 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 CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of 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, Institutional Review Boards (IRB)/Independent Ethics Committees (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.

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

A 2 Financial Disclosure

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

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the 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.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the

samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

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

Not applicable.

A 6 Dissemination of Clinical Study Data

A description of this clinical study 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 electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of 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.
- 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. The first act of recruitment is the first site open and will be the study start date.

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of 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 IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a 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.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An adverse event is the development of any untoward medical occurrence in a participant 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 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-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly 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 (AEs) 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 chronic lymphocytic leukaemia into diffuse large B-cell lymphoma) 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, etc.) or convulsions that do not result in hospitalisation.
- Development of drug dependency or drug abuse.

Intensity Rating Scale:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

The grading scales found in the revised National Cancer Institute CTCAE version 5.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE 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.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. 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 IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTMS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTMS - 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 standard of care medication in open label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a 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 organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900:

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name

- UN 3373 – Biological Substance, Category B
- 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 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 CCI 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.

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
  - Healthy Volunteers and paediatric participant 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 CCI sample for this genetic research will be obtained from the participants after randomisation at the visit specified in the relevant module SoA. 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 at the planned visit, 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 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 organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. 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, 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 organisations to analyse the samples.
- AstraZeneca and its designated organisations 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 organisations 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.

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 TBL from a local laboratory.

The investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (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 SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law
Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3 × Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law
AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating

cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Central Laboratories Being Used:

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to AstraZeneca representative).

The investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the investigator will:

- Notify the AstraZeneca representative.
- Request a repeat of the test (new blood draw) by the central laboratory without delay.
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result.

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the participant meets PHL criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

Local Laboratories Being Used:

The investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative.
- Determine whether the participant meets PHL criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the 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 of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- 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 Potential Hy's Law SAE 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 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:

- 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

Hy's Law Lab Kit for Central Laboratories	
Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV
	HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)[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

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Appendix F Abbreviations

Abbreviation or special term	Explanation
1QW	once weekly dosing
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AITL	angioimmunoblastic T-cell lymphoma
ALCL	anaplastic large cell lymphoma
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid lymphoma
AST	aspartate aminotransferase
β-HCG	beta-human chorionic gonadotropin
CCI	CCI
BV	brentuximab vedotin
CAR-T	chimeric antigen receptor T-cell
CDK9	cyclin dependent kinase 9
CHF	congestive heart failure
cHL	classical Hodgkin Lymphoma
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPK	creatine phosphokinase
CR	complete response
CRO	Contract Research Organisation
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCO	data cut-off
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DoR	duration of response
DUS	disease under study
EBV	Epstein–Barr virus

Abbreviation or special term	Explanation
ECG	electrocardiogram
ECHO	echocardiograms
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin embedded
FIH	first-in-human
FU	follow-up
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GLDH	glutamic dehydrogenase
GVHD	graft-versus-host disease
HBV	hepatitis B virus
HCP	Health Care Professional
HIV	human immunodeficiency virus
HL	Hy's Law
HSCT	haematopoietic stem cell transplantation
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
INR	International Normalised Ratio
IP	investigational product
IRB	Institutional Review Board
IRT/RTSM	Interactive Response Technology System/Randomisation and Trial Supply Management
ITT	intention-to-treat
IV	intravenous
KM	Kaplan-Meier

Abbreviation or special term	Explanation
LDH	serum lactate dehydrogenase
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MCL1	myeloid cell leukaemia 1
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
CCI	CCI
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NK	natural killer
NKTCL	natural killer/T-cell lymphoma
OAE	other significant adverse event
ORR	overall response rate
OS	overall survival
CCI	CCI
CCI	CCI
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression free survival
PHL	potential Hy's Law
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
PR	partial response
PTCL	peripheral T-cell lymphoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase II dose
r/r	relapsed/refractory
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCT	stem cell transplantation
SD	stable disease
SoA	schedule of activities
SoC	standard of care
SOI	start of infusion

Abbreviation or special term	Explanation
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 vendor
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	Unites States
WOCBP	women of childbearing potential

Appendix G 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 hypouricaemic 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 assumes the laboratory evidence of metabolic changes and significant clinical toxicity that requires clinical intervention. Clinical tumour lysis syndrome is defined as the presence of laboratory tumour lysis syndrome and any 1 or more of the below-mentioned criteria. Maximal clinical tumour lysis syndrome 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
Cardiac Arrhythmia*	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled	Life-threatening (eg, arrhythmia	Death

				medically or controlled with devise (eg, defibrillator)	associated with CHF, hypotension, syncope, shock)	
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 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 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 HCP from the study site or TPV service will visit the participant's home / or other remote location as per local 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.

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