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

Dizal (Jiangsu) Pharmaceutical Co., Ltd

Address: 199 Liangjing Road, Zhangjiang High-Tech Park, Shanghai, China

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Sponsor: Dizal (Jiangsu) Pharmaceutical Co., Ltd

Dizal Research and Development

Site representative

[redacted]

INVESTIGATOR STATEMENT

Protocol Number: DZ2019J0005

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

I understand that all information concerning AZD4205 in connection with this study and not previously published is confidential. This confidential information includes the Investigator's Brochure, Clinical Study Protocol, Case Report Form, clinical methodology, and basic scientific data.

I will not initiate this study without approval from the Institutional Review Board/Ethics Committee and I understand that any changes in the protocol must be approved in writing by Dizal (Jiangsu) Pharmaceutical Co., Ltd and the Institutional Review Board/Ethics Committee before they can be implemented, except when necessary to eliminate immediate hazards to the subjects.

By my signature below, I attest that I have read, understand, and agree to abide by all the conditions, instructions, and restrictions contained in Protocol Number DZ2019J0005, and will conduct the trial in accordance with Good Clinical Practice (GCP) and applicable regulatory requirements.

_____

Investigator's Printed Name

_____ _____

Investigator's Signature Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Study protocol	Date
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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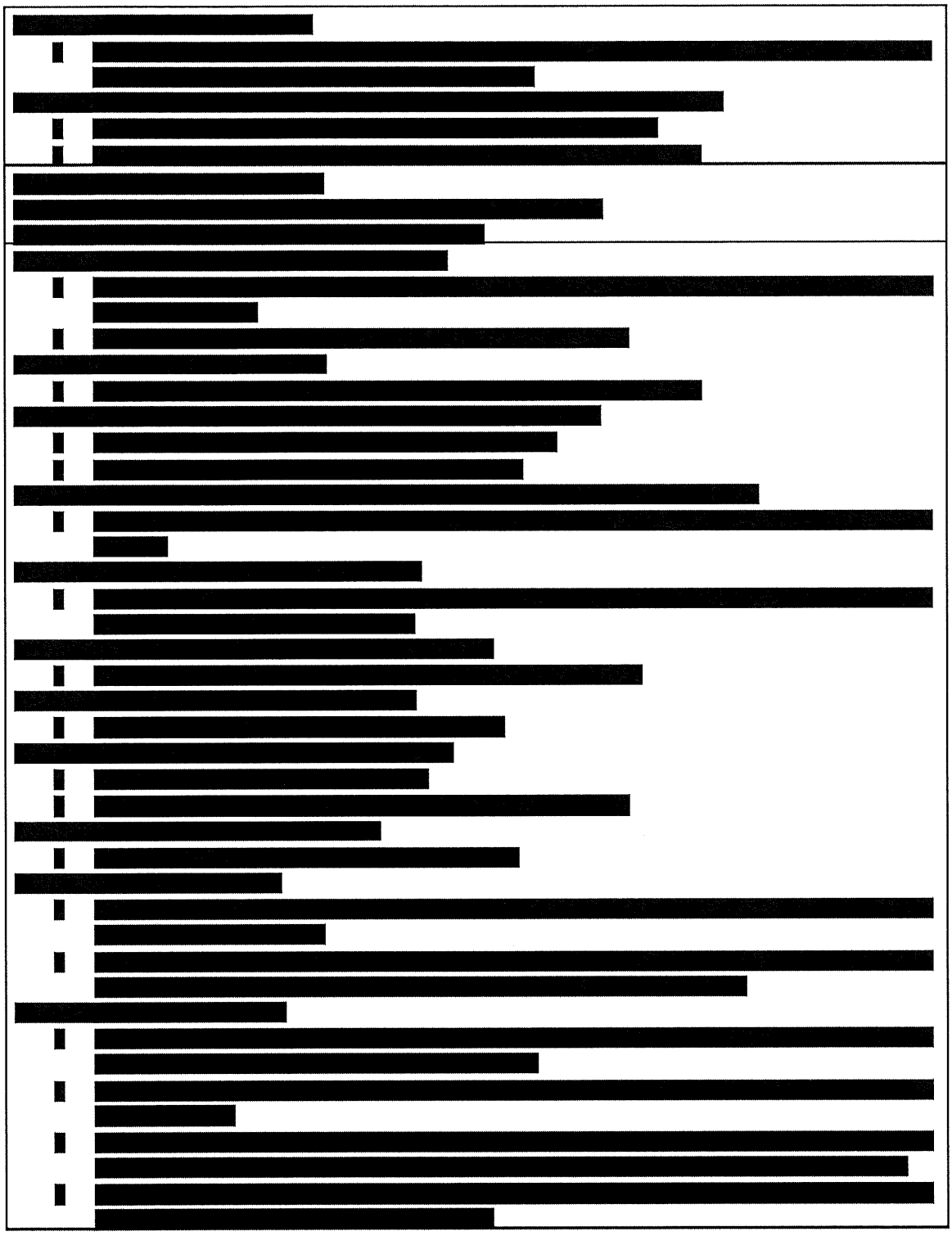
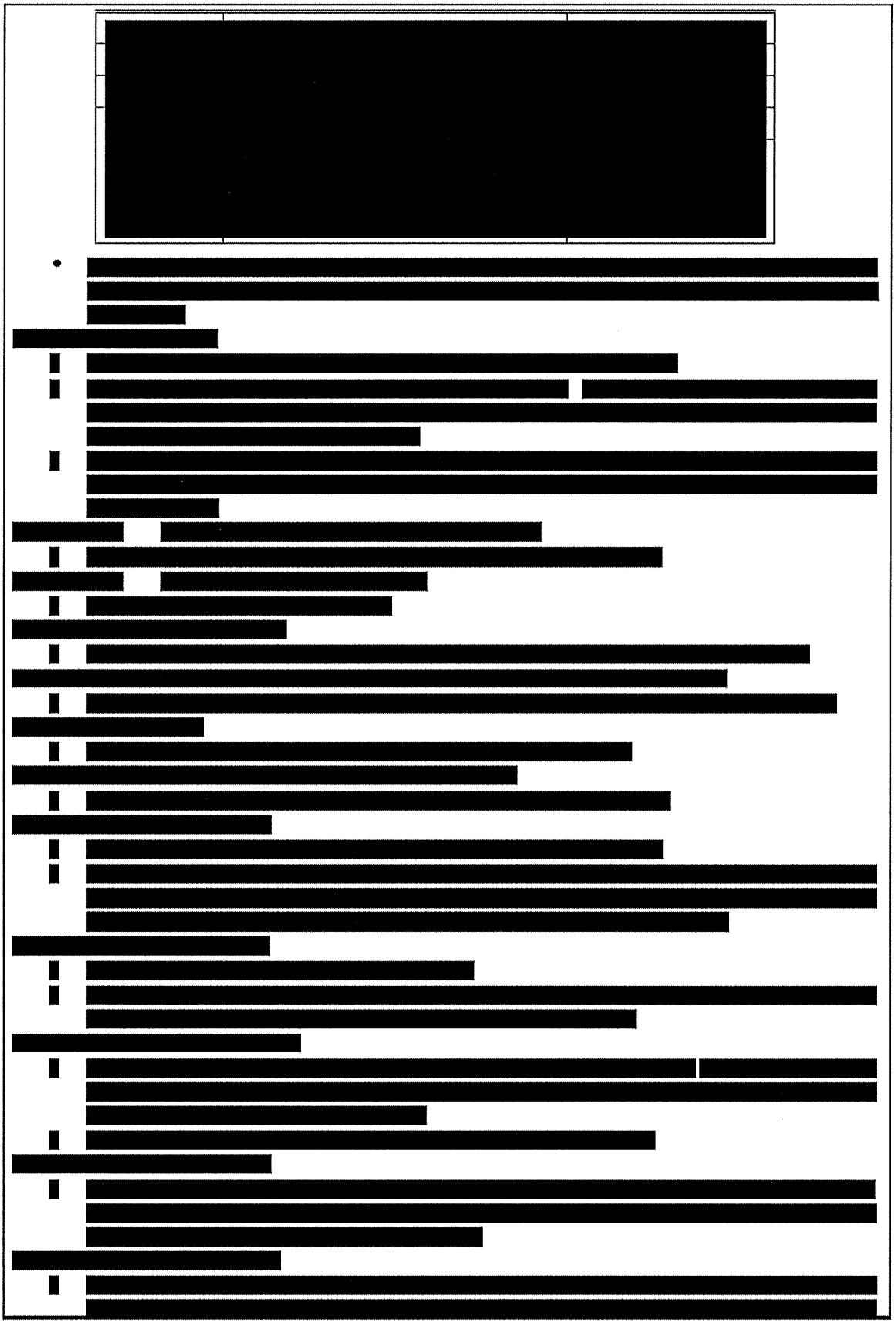
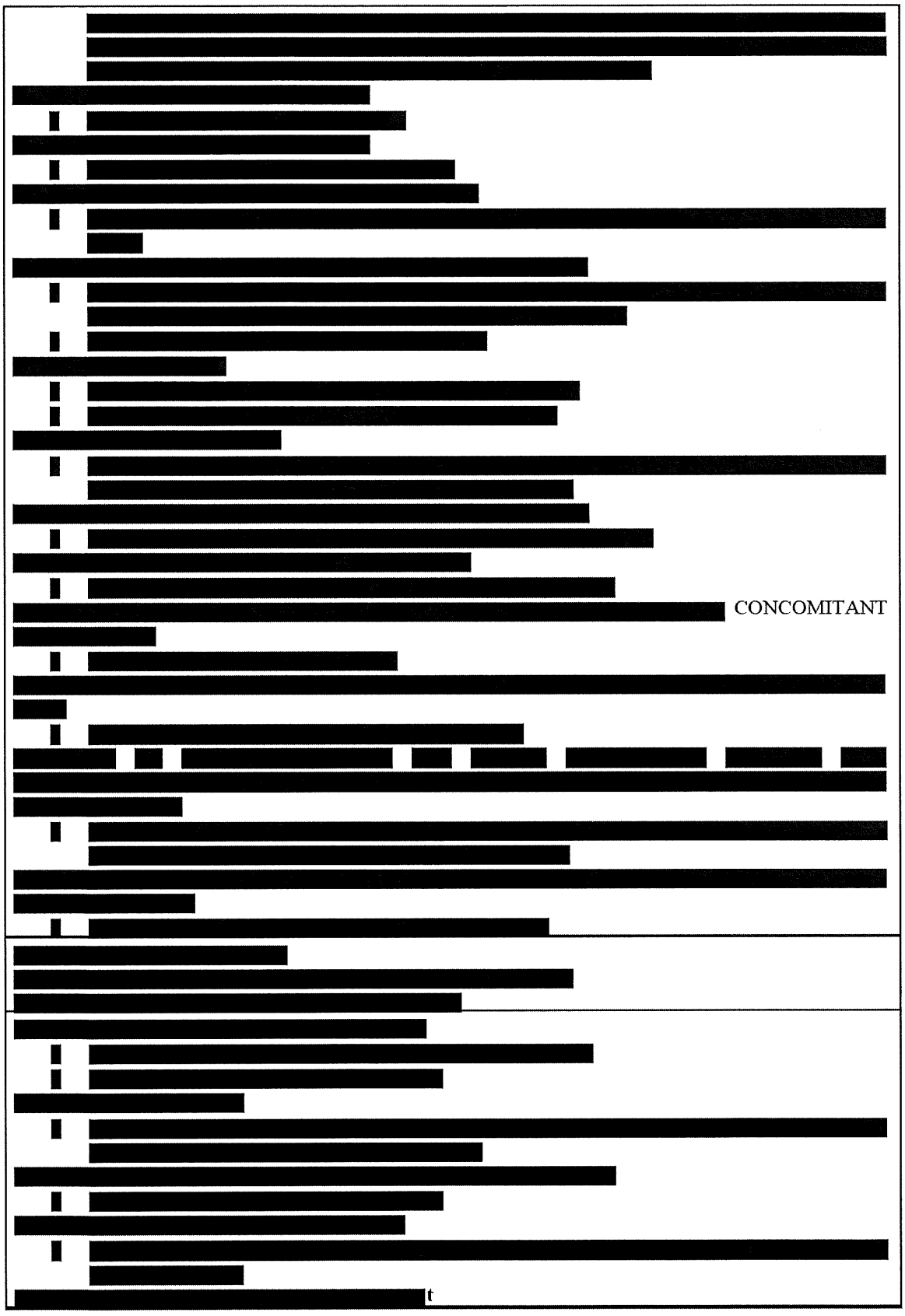





CONCOMITANT

INTRODUCTION & STUDY FLOW CHART

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

Constitutive activation of Janus kinase (JAK)/signal transducer and activation of transcription (STAT) pathways is associated with a wide variety of malignancies, including non-small cell lung cancer (NSCLC) and hematological malignancies. For example, elevated phospho-STAT3 (pSTAT3, Y705) is observed in tumors with EGFR activating mutations, and is linked to poor prognosis or response to a variety of anti-EGFR therapies in lung cancer. For hematological malignancies, it was reported in ASH 2018 annual meeting that inhibition of JAK/STAT pathway by Ruxolitinib, a JAK1/JAK2 inhibitor, showed promising anti-tumor activity in patients with Peripheral T Cell Lymphoma (PTCL), especially PTCL patients with JAK/STAT pathway aberrations (Moskowitz AJ et al. 2018). Thus, inhibition of JAK/STAT pathway is an attractive therapeutic approach for patients with NSCLC or PTCL.

AZD4205 is an oral, potent and highly selective JAK1 inhibitor with greater than 200-fold selectivity over other JAK family kinases. AZD4205 inhibits pSTAT3 (Y705) with an IC_{50} (half maximal inhibitory concentration) of [redacted] in HuT102 T cell lymphoma cells harboring JAK/STAT pathway aberration, and GI_{50} (half inhibitory concentration of cell proliferation) of [redacted]. In preclinical T cell lymphoma xenograft models in mice, AZD4205 exhibited dose-dependent anti-tumor efficacy. These data provide preclinical evidence to support clinical development of AZD4205 in patients with PTCL.

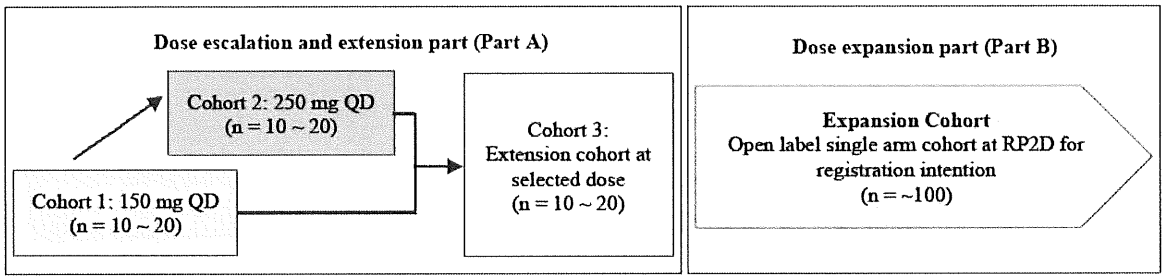
Exposure of AZD4205 increased roughly proportionally with dose in rats and dogs, with no apparent sex difference. *In vitro* data suggests that metabolic clearance of AZD4205 is primarily via both CYP3A and FMOs 1 and 3. This spread of metabolic routes may mitigate the risk of co-administration of medications known to be P450 perpetrators. The drug metabolism and pharmacokinetic (PK) profile described supports AZD4205 progressing into the intended target patient population.

The key findings from nonclinical toxicology studies include: [redacted]

[redacted]. The results from nonclinical toxicology studies support progression of AZD4205 into the clinical trials in patients with advanced cancer.

Following the first-time-in-human (FTIH) study in Australia (DZ2017J0001, clinicaltrials.gov identifier: NCT03450330) and phase I study in healthy volunteers in US (DZ2018J0001, clinicaltrials.gov identifier: NCT03728023), this phase I/II study is to evaluate AZD4205 monotherapy at defined doses in PTCL patients. PTCL patients who relapsed from or are refractory to standard systemic therapy, or who are intolerant to standard systemic therapy will be enrolled to investigate the safety, tolerability and anti-tumor efficacy of AZD4205. AZD4205 will be administered at two dose levels, 150 mg and 250 mg once daily, respectively.

STUDY FLOW CHART



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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation	Explanation
AE	Adverse event (see definition in Section 6.5.1)
AITL	Angioimmunoblastic T-cell lymphoma
ALCL	Anaplastic large-cell lymphoma
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APD_{90}	Cardiac action potential, duration of 90% repolarization
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC_{0-24h}	Area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{0-t}	Area under the plasma concentration-time curve from time 0 to the last measurable concentration
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 to the infinity
AUC_{ss}	Area under plasma concentration-time curve during any dosing interval at steady state [amount· time/volume]
BCRP	Breast cancer resistance protein
BCVA	Best corrected visual acuity
BP	Blood pressure
CIs	Confidence intervals
CL	Clearance
CL/F	Total body clearance of drug from plasma after an oral dose
CL_{ss}/F	Total body clearance of drug from plasma after an oral dose at steady state
C_{max}	Maximum plasma concentration
CR	Complete response
CMR	Complete metabolic response
CMV	Cytomegalovirus
CRF	Case Report Form (electronic/paper)
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
$C_{ss,max}$	Maximum (peak) steady state drug concentration in plasma during dosing interval [amount/volume]
$C_{ss,min}$	Minimum (trough) steady state drug concentration in plasma during dosing interval [amount/volume]
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumor DNA
cTnT	Cardiac troponin T
DCR	Disease Control Rate

Abbreviation	Explanation
DDI	Drug-Drug Interaction
DLCO	Diffusing capacity of the lungs for carbon monoxide
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DRF	Dose range finding
DVT	Deep vein thrombosis
EATL	Enteropathy-associated T-cell lymphoma
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECIL	European Conference on Infections in Leukemia
ECG	Electrocardiogram
Echo	Echocardiogram
ECOG	Eastern Co-operative Oncology group
EGFR	Epidermal growth factor receptor
EGFRm	Epidermal growth factor receptor mutant
^{18}F-FDG PET	^{18}F-Fludeoxyglucose Positron emission tomography
FMO	Flavin-containing monooxygenase enzyme
FVC	Forced vital capacity
GI	Gastro-intestinal
GI_{50}	Half inhibitory concentration of cell proliferation
GCP	Good Clinical Practice
hADME study	Human Absorption-Distribution-Metabolism-Excretion study
HDAC	Histone deacetylases
HED	Human equivalent dose
HNSTD	Highest non-seriously toxic dose
HR	Heart rate
HRCT	High-resolution computed tomography
HSTCL	Hepatosplenic T-cell lymphoma
IB	Investigators Brochure
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IL-6	Interleukin 6
IRC	Independent review committee
JAKs	Janus kinases
Ki	Inhibition constant
LIMS	Laboratory information management system
LVEF	Left ventricular ejection fraction
MAD	Maximum absorbable dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging

Abbreviation	Explanation
MRT	Mean residence time
MTD	Maximum tolerated dose
MUGA	Multigated Blood Pool Analysis
NE	Not evaluable
NF-κB	Nuclear factor-κB
NGS	Next generation sequencing
NK/TCL	Natural killer/T-cell lymphoma
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NSCLC	Non-Small Cell Lung Cancer
NTL	Non-target lesion
OATP	Organic anion transport protein
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCP	Pneumocystis carinii pneumonia
PD	Progression of disease
PE	Pulmonary embolism
PFS	Progression free survival
PFTs	Pulmonary function tests
P-gp	P-glycoprotein
PJP	Pneumocystis jiroveci pneumonia
PK	Pharmacokinetics
PK/PD modeling	Pharmacokinetic/pharmacodynamic modelling
PR	Partial response
PMR	Partial metabolic response
pSTAT	Phospho-signal transducer and activation of transcription
PCP	Pneumocystis carinii pneumonia
PTCL	Peripheral T Cell Lymphoma
PTCL-NOS	Peripheral T Cell Lymphoma-not otherwise specified
ONCE DAILY	Once daily
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QTc Fredericia
RP2D	Recommended Phase 2 doses
SAE	Serious adverse event
SD	Stable disease
SoC	Standard of care
SRC	Safety Review Committee
STAT	Signal transducer and activation of transcription
STD_{10}	10% of the Severely Toxic Dose in rodents
TEAE	Treatment emergent adverse event

Abbreviation	Explanation
TYK2	Tyrosine kinase 2
λz	Smallest (slowest) disposition (=hybrid) rate constant [time^{-1}]
$t_{½}$	Half-life
$t_{½\lambda z}$	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve [time]
TB	Tuberculosis
TKI	Tyrosine kinase inhibitor
TL	Target lesion
TLC	Total lung capacity
t_{max}	Time to maximum plasma concentration
$t_{ss\ max}$	Time to maximum plasma concentration at steady state
ULN	Upper limit of normal (the high limit of a reference range)
VA	Visual acuity
V_{ss}/F	Volume of distribution (apparent) at steady state after an oral dose
WBDC	Web Based Data Capture

1. STUDY OBJECTIVES

This is a Phase I/II study to evaluate the safety, tolerability, pharmacokinetics and anti-tumor efficacy of AZD4205 in patients with relapsed or refractory peripheral T cell lymphoma (r/r PTCL).

1.1 Part A (Dose escalation and extension cohorts)

Primary objectives

Primary objectives	Outcome measure
• To assess the safety and tolerability of AZD4205 in patients with r/r PTCL	• Adverse events (graded by CTCAE version 5.0)

Secondary objectives

Secondary objectives	Outcome measure
• To investigate anti-tumor efficacy of AZD4205 when given orally to patients with PTCL who relapsed from or are refractory/intolerant to standard systemic therapy.	• Objective response rate (ORR), duration of response (DoR), and progression free survival (PFS) using investigator assessments according to the 2014 Lugano classification
• To characterize the pharmacokinetics (PK) of AZD4205 in plasma	• PK parameters derived from plasma concentrations of AZD4205 Data from this study may form part of a pooled analysis with data from other studies

[redacted]

[redacted]

[redacted]

1.2 Part B (Dose expansion cohort)

Primary objectives

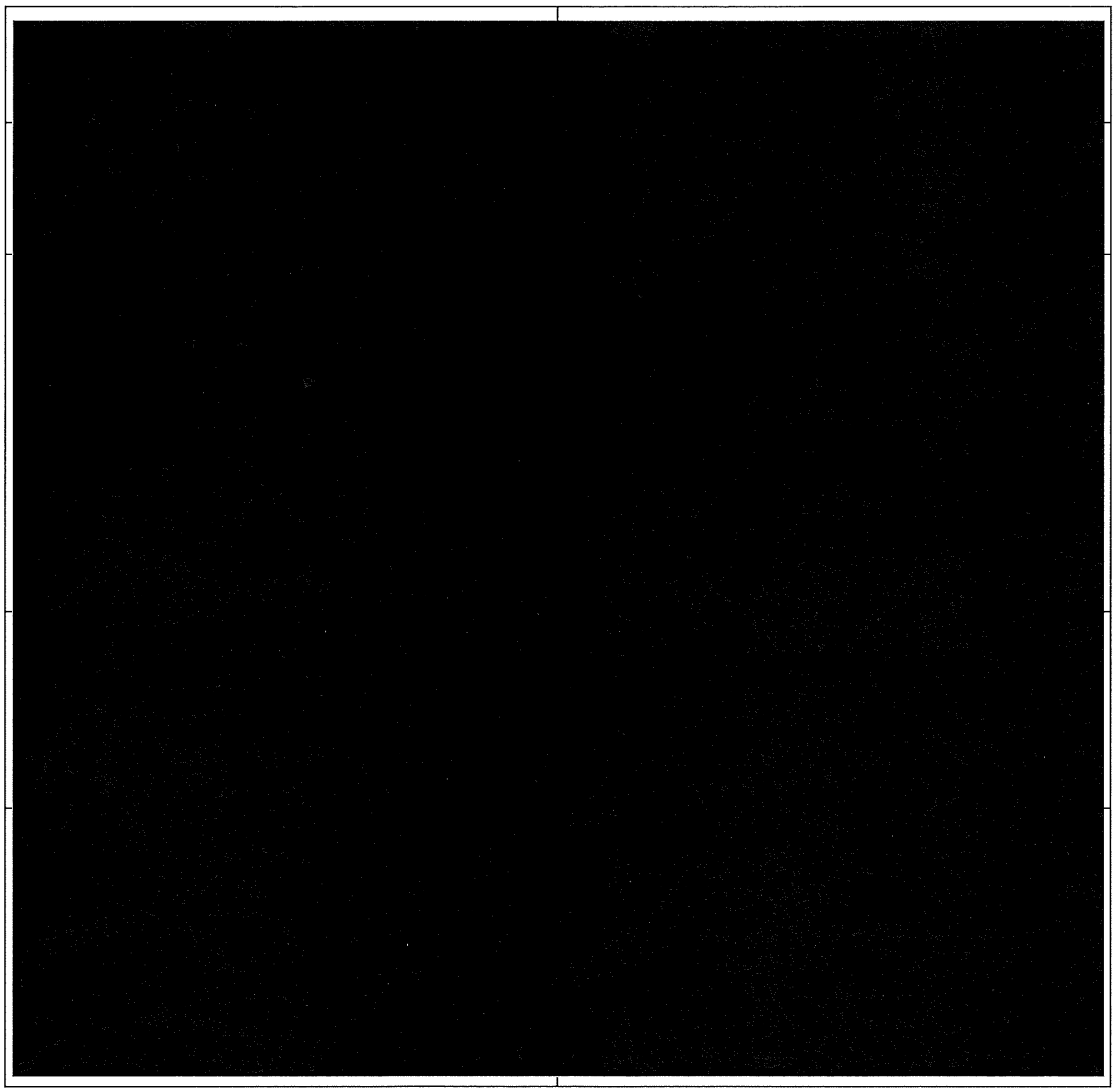
Primary objectives	Outcome measure
• To assess the anti-tumor efficacy of AZD4205 using CT-based objective response rate (ORR) as primary efficacy endpoint in patients with r/r PTCL	• CT-based ORR by independent review committee (IRC), according to 2014 Lugano classification

Secondary objectives

Secondary objectives	Outcome measure
• To assess the anti-tumor efficacy of AZD4205 using other CT-based efficacy endpoints in patients with r/r PTCL	• DoR, complete response rate (CRR), PFS, and time to response (TTR) assessed by IRC based on CT imaging, according to 2014 Lugano classification • Investigators-assessed efficacy endpoints based on CT imaging per Lugano criteria
• To assess the safety and tolerability of AZD4205 in patients with r/r PTCL	• Adverse events (graded by CTCAE version 5.0)
• To characterize the PK of AZD4205 in plasma	• PK parameters derived from plasma concentrations of AZD4205 Data from this study may form part of a pooled analysis with data from other studies

[redacted]

[redacted]



2. BACKGROUND

2.1 Peripheral T-cell lymphoma (PTCL) and biologic role of JAK/STAT pathway in cancer

PTCL represents approximately 10%-25% of non-Hodgkin lymphoma and is a heterogeneous disease with broad morphological spectrum and immunophenotypic variations among patients (Gaulard P et al. 2014). For most subtypes of PTCL, except anaplastic large cell lymphoma (ALCL), the frontline treatment regimen is typically combination chemotherapy and refractory regimen is the histone deacetylase inhibitors. However, these treatments often just offer limited clinical benefit with ORR of ~30% and PFS of only 3~4 months (Moskowitz AJ et al. 2017). Although Brentuximab Vedotin is approved for CD30 positive systemic ALCL, targeted therapy for the most common PTCL

subtypes is still lacking. Thus, there is an unmet need for new targets and treatment options both in upfront and relapsed settings of PTCL.

The Janus kinases (JAKs) are a family of intracellular tyrosine kinases of the class I and II receptor superfamily that consists of four members; JAK1, JAK2, JAK3 and Tyrosine kinase 2 (TYK2). Activation of JAKs occurs when a cytokine binds to its receptor, inducing multimerization of receptor subunits that brings JAKs into proximity with each other for transactivation. Activated JAKs then phosphorylate signal transducer and activation of transcription (STAT) proteins, resulting in their dimerization. Phosphorylated STAT dimers translocate to the nucleus to modulate JAK/STAT target gene expression. Thus, JAKs play a critical role in the JAK/STAT signaling cascade to transmit information from extracellular cytokine cues to the nucleus, leading to DNA transcription and expression of genes that are involved in immunity, proliferation, differentiation, apoptosis and oncogenesis (Buchert M et al. 2016).

The critical roles of JAK and STAT proteins in hematopoietic oncology have been demonstrated (Khwaja A. 2006), and JAK/STAT pathway aberrations associated with poor prognosis in lymphoma has been reported (Han JJ et al. 2018). The activation or aberration of JAK/STAT pathway is considered as a therapeutic target for several aggressive cancers, including various solid tumors, leukemia, and lymphoma (Han JJ et al. 2018, Kucuk C et al. 2015). Inhibition of JAK/STAT pathway by ruxolitinib, a JAK1/JAK2 inhibitor, showed promising anti-tumor activity in patients with PTCL, especially PTCL patients with JAK/STAT pathway aberrations (Moskowitz AJ et al. 2018).

Constitutive activation of JAK/STAT pathways is also associated with a wide variety of solid tumors and are implicated in tumor escape from chemo- and targeted- therapies (Tezcanli KB et al. 2014, Kim SM et al. 2012). For example, elevated phospho-STAT3 (pSTAT3, Y705) is observed in tumors with EGFR activating mutations, and is linked to poor prognosis or response to a variety of anti-EGFR therapies in lung cancer (Gao SP et al. 2008, Song L et al. 2011). In addition, the JAK1/STAT3 pathway is further activated in response to EGFR blockade by tyrosine kinase inhibitor (TKI) in EGFR lung cancer models to drive tumor cell survival and residual disease. This typically arises from the induction of IL-6 via NF-κB pathway activation induced by TKIs, resulting in autocrine JAK1/STAT3 pathway activation (Blakely CM et al. 2015, Gao SP et al. 2008, Song L et al. 2011). Thus, inhibition of JAK/STAT pathway is an attractive therapeutic approach to overcome the resistance to standard TKIs therapy.

Thus, inhibition of JAK/STAT pathway is an attractive therapeutic approach for patients with PTCL or NSCLC.

2.2 Investigation agent

AZD4205 is a potent, ATP-competitive inhibitor of JAK1 kinase with an inhibition constant (Ki) of [redacted]. It exhibits greater than 200-400 fold of selectivity over other JAK family kinases and has a favorable selectivity profile across the kinome. AZD4205 inhibits pSTAT3 (Y705) with an IC_{50} of [redacted] in HuT102 T-cell lymphoma cells harboring JAK/STAT pathway aberration. It also demonstrates effective inhibition of tumor cell

proliferation with GI_{50} of [redacted] in this cell line. In preclinical animal models, AZD4205 exhibited durable pSTAT3 inhibition and anti-tumor activity.

2.3 Non-clinical information and correlative studies of AZD4205

2.3.1 The key data from primary pharmacology studies

- AZD4205 is a potent and selective ATP-competitive JAK1 kinase inhibitor with a Ki of [redacted]. When tested for selectivity against an in vitro panel of 273 kinases, eight other kinases were inhibited by greater than 50% with 1 μM of AZD4205 (ranging from 52-88% inhibition), whereas JAK1 was near completely inhibited with 97% inhibition.
- AZD4205 is selective for JAK1 among JAK family demonstrating greater than 200-fold selectivity over JAK2, and 400 fold over JAK3 and TYK2 in enzyme assays. The selectivity over JAK2 is verified using TEL-JAK2 Ba/F3 spleen tumor *in vivo*.
- In human peripheral blood mononuclear cell (PBMC), AZD4205 inhibited IL-6 stimulated pSTAT3 with an IC_{50} of [redacted]
- AZD4205 inhibits pSTAT3 (Y705) with an IC_{50} of [redacted] in HuT102 T-cell lymphoma cells harboring JAK/STAT pathway aberration. It also demonstrates effective inhibition of tumor cell proliferation with GI_{50} of [redacted] in this cell line.
- *In vivo*, AZD4205 showed potent anti-tumor activity in T-cell lymphoma xenograft generated by HuT102 cell model. Dose-dependent anti-tumor effect was observed, and tumor regression was achieved with AZD4205 at 40 mg/kg once daily or 20 mg/kg, 40 mg/kg twice daily. In this model, AZD4205 induced sustained pSTAT3 inhibition with a good pharmacokinetics / pharmacodynamics / efficacy correlation.

2.3.2 The key findings in the secondary and safety pharmacology studies

- In a secondary pharmacology panel of 188 molecular targets, AZD4205 had activity (a defined IC_{50} value) against 28 targets. No targets had activity within 30-fold of the binding JAK1 Ki [redacted]
- AZD4205 inhibited the hERG potassium channel with an IC_{50} of [redacted]. In an action potential assay using cardiomyocytes derived from human induced pluripotent stem cells, [redacted] μM AZD4205 increased the action potential duration (APD90) following both acute (0.5 hours) and longer term (6 and 24 hours) incubation by up to [redacted]%.
- Single (oral) administration of AZD4205 to conscious telemetered dogs resulted in the following cardiovascular effects at all doses (30, 60 and 100 mg/kg): Increases in QTca interval up to 32 hours post-dose (6%, 13 ms at 100 mg/kg); decreases in dP/dt+ (an index of cardiac contractility, up to 23% at 30 and 60 mg/kg), up to 12 hours post-dose. The lowest effect level for effects on the cardiovascular system was 30 mg/kg (plasma concentration at 4 hours post-dose of [redacted] total, [redacted] free). Increases in QTca interval were also observed in the dog 1-month toxicity study.

- In a rat telemetry study, oral administration with AZD4205 at 150 mg/kg caused an increase in blood pressure, with a maximum increase of 15% in diastolic blood pressure. The No Observed Effect Level (NOEL) for effects on the cardiovascular system was 50 mg/kg (plasma concentration at 4 hours post-dose of [redacted].
- In a rat modified Irwin screen, irregular breathing and wheezing was noted following oral administration of AZD4205 at 50 mg/kg and 150 mg/kg. The NOEL was considered to be 25 mg/kg (plasma concentration at 6.5 hours post-dose of [redacted]
- In rat respiratory study, oral administration AZD4205 was associated with a dose-dependent decrease in tidal volume at $\geq$ 50 mg/kg up to 12.7%. Increases in respiratory rate (up to 25.2%) and decreases in inspiration and expiration time (up to 20.0% and 16.7%, respectively) were observed at 150 mg/kg. The NOEL was considered to be 25 mg/kg (plasma concentration at 6.5 hours post-dose of [redacted]
- All of the effects observed in the in vivo safety pharmacology studies were reversible.

2.3.3 Non-clinical pharmacokinetics

- AZD4205 exhibited consistent plasma protein binding across concentrations (0.1 - 100 μM) in rat and mouse (mean rat: 37.9%, mean mouse: 40.9%). In dog there was a trend for lower binding as concentration increased (range, 38.7 - 49.3% unbound). In rabbit, the percent unbound was lower when compared to other species (mean 18.7% unbound). AZD4205 mean human unbound percentage across concentrations (0.1 - 100 μM) was [redacted]
- During *in vitro* incubation with human hepatocytes, AZD4205 was found to be metabolized to a single oxidative metabolite. In a heterologous expressed enzyme system, CYP3A4 was found to be the predominant P450 isoform involved in the metabolism of AZD4205, accounting for [redacted] of its metabolism mediated by P450. CYP2A6, CYP2C8, CYP2C9 and CYP3A5 were also involved in the metabolism of AZD4205, although these account for only 0.199%, 1.05%, 0.380% and 9.16% of the overall P450 mediated metabolism, respectively. In other in vitro studies, flavin-containing monooxygenase enzyme (FMO) was also shown to metabolize AZD4205 and contribute between [redacted] of the overall liver microsomal metabolism.
- At clinically relevant concentrations, AZD4205 is unlikely to cause clinically significant DDIs via cytochrome P450 enzymes. No significant reversible or time-dependent inhibition was observed *in vitro*, i.e. IC_{50}s could not be determined. In a cell-based assay, AZD4205 did not significantly induce P450 mRNAs. DDI risk when AZD4205 acts as CYP inducer is considered low at clinically relevant concentrations.

- AZD4205 had weak inhibition on the drug transporters, P-gp, OAT1 and OAT3 (IC_{50} >100 μM), and moderate inhibition on BCRP, OATP1B1, OCT2, MATE1 and MATE2-K (IC_{50}s of [redacted], respectively). Secondly, exposure of those co-medications whose disposition depends on kidney MATE1 and MATE2-K could not be fully ruled out at clinically relevant exposure.

2.3.4 The key findings in the toxicity studies

- In dogs, dose-limiting toxicities were multiple adverse signs (including decreased activity, dehydration, weak, abnormality feces, skin lesions, hunched posture), along with histopathological observations in gastro-intestinal tract (from esophagus to rectum), thymus, spleen, lung, pancreas, urinary bladder, GALT and/or lymph nodes, bone marrow, liver, skin and subcutis. In rats, noisy respiration, pilo-erection, skin lesion, trembling, thin and pale, along with histopathologic observations in the bone marrow, lung, lymph nodes, thymus, GALT and spleen were considered dose-limiting toxicity.
- In the repeat dose toxicology studies, a dose-related incidence of minimal cardiac myofiber degeneration and necrosis was observed in rats at dose levels ≥ 7.5 mg/kg/day following daily oral dosing for up to 4-week. In the pivotal 4-week rat study, this finding was not present following 4-week off-dose, indicating complete reversibility. In 13-week rat study, myocyte degeneration or chronic myocarditis (minimal in all cases) was seen in the heart of both sexes given AZD4205. Myocyte degeneration was also seen in one control male killed at the end of the treatment and treatment free periods. Given the very minimal, focal nature of this change it is considered that the increased incidence in treated animals represents a sampling variation, and not an effect of AZD4205. No cardiac pathology was observed after daily administration of AZD4205 in rats for 26-week at doses up to 30 mg/kg/day, in dogs for 4-week, 13-week or 39-week at doses up to 15 mg/kg/day.
- In dogs, minimal to moderate erosions/ulcerations in the stomach and, small and large intestines were noted at doses ≥ 45 mg/kg/day in the MTD/Dose range finding (DRF) study following dosing for 14 days. Other GI findings included inflammatory infiltrates in the stomach and hemorrhage throughout the GI tract at doses ≥ 20 mg/kg/day and minimal to mild villous atrophy at ≥ 45 mg/kg/day. Minimal to moderate inflammatory infiltrates in the intestine were noted in the dog 4-week pivotal study at doses ≥ 10 mg/kg/day and these changes were completely reversed at the end of the 4-week recovery period. Minimal congestion in ileo-cecal junction and slight inflammation within the jejunum were noted in 13-week dog study at 15/9 mg/kg/day.
- In rats, minimal accumulation of eosinophilic material in alveolar spaces of the lung was noted in the 28-day rat DRF study at doses ≥ 50 mg/kg/day and in the pivotal 4-week study at 75 mg/kg/day. Increased alveolar macrophages were also noted in the 4-week pivotal study at doses ≥ 7.5 mg/kg/day. These findings were not present at the end of the 4-week recovery period, except for the increases in alveolar macrophages in female rats, indicating partial reversibility of lung findings in rat. In 13-week or 26-week rat study, minimal to moderate foamy alveolar macrophages

and alveolar proteinosis/lipoproteinosis were noted in rats given 3, 4, 15, 30 or 50 mg/kg/day AZD4205 in a dose dependent manner. In dogs, minimal to mild mixed inflammatory infiltrates were noted in the MTD/DRF study at doses ≥ 45 mg/kg/day, but there were no AZD4205-related lung findings in the 4-week , 13-week or 39-week pivotal dog studies up to the highest dose of 15 mg/kg/day.

- In dogs, minimal to moderate hepatocyte degeneration/necrosis accompanied by mixed or neutrophilic inflammatory infiltrates in the liver was noted in the MTD/DRF study at doses ≥ 20 mg/kg/day. In the 4-week pivotal study, minimal mixed/neutrophilic inflammatory infiltrates were noted at 15 mg/kg/day, and persisted in one female dog following the 4-week recovery period. In the 13-week dog GLP study, dogs given 3, 9 or 15/9 mg/kg/day had dose-dependent minimal-to-slight extramedullary hemopoiesis within the liver, which was reversible. In the rat, minimal single cell necrosis was seen at the non-tolerated dose of 200 mg/kg/day. Histopathology findings were correlated with reversible increases in plasma AST, ALT, ALP at doses ≥ 15 mg/kg/day, and increased bilirubin at doses ≥ 20 mg/kg/day.
- Skin lesions were observed in both rats and dogs, which were the secondary effect of the immunosuppressive effects of AZD4205. In 13-week repeat dose rat study, wet lesions around the mouth were noted in rats at 50 mg/kg/day. In 39-week repeat dose dog study, various skin lesions (hair loss, rash, erythema, raised areas, thickening, encrustations and exfoliation) were noted in multiple regions (including the muzzle, thorax, abdomen and limbs and in some dogs the whole body was affected) at 4 and 7 mg/kg/day. In addition, the formation of wart-like growths and/or wet abrasions on limbs (often between digits), muzzle, eyelids and buccal cavity were observed. After treated with drug (Simparcia), the skin lesions significantly improved.
- Dose-dependent decreased bone marrow cellularity with correlating decreases in white blood cell, reticulocytes and red cell mass (red blood cell counts, hemoglobin and hematocrit) parameters, were noted in rats at dose levels ≥ 7.5 mg/kg/day and in dogs at dose levels ≥ 20 mg/kg/day in 4-week GLP studies, and one dog given 15/9 mg/kg/day in 13-week dog GLP study, and in rats at dose levels ≥ 3 mg/kg/day in 26-week GLP study. All microscopic and hematological changes showed partial (lymphocytes in the rat, neutrophils, monocytes, and red cell mass in dogs) or complete (all other findings) recovery.
- Dose-dependent hypocellularity was noted in the thymus, spleen, lymph nodes, and GALT in rat MTD/DRF and 4-week studies at doses ≥ 7.5 mg/kg/day, in 13-week rat study (≥ 4 mg/kg/day) and in 26-week rat study (≥ 3 mg/kg/day). These changes reversed following the recovery period with exception of lymphocyte counts, which showed partial recovery. Similar pathology and hematology changes were seen in the dog MTD/DRF and 4-week studies at doses ≥ 5 mg/kg/day, with decreased lymphocyte counts at doses ≥ 10 mg/kg/day. The lymphocyte counts fully or partially recovered following 4-week off-dose. Dose-dependent minimal-to-severe decreased general cellularity within the lymph node and thymus, slight-to-moderate increase in extramedullary hemopoiesis within spleen were noted in 13-week dog

study (≥ 3 mg/kg/day). Minimal to marked generalized decreased cellularity in lymph node and thymus were noted in 39-week dog study (≥ 1 mg/kg/day). Above findings were not present in recovery dogs.

- AZD4205 was negative in the GLP Ames test, in vitro chromosome aberration assay in Chinese hamster lung (CHL) cells, and an in vivo micronucleus assay in rats. An impurity in the AZD4205 drug substance, AZ13829510, was found to be mutagenic in the Ames test.
- AZD4205 showed no evidence of phototoxic potential in an *in vitro* 3T3 phototoxicity assay conducted in the presence and absence of UV light.
- The results from these toxicology studies support clinical trials with AZD4205 in patients with advanced cancer.

Further details are provided in the Investigators' Brochure (IB).

2.4 Clinical experience of AZD4205

At the effective date of this version of protocol, two clinical studies for AZD4205 were completed, including study DZ2017J0001 and study DZ2018J0001.

Study DZ2017J0001 (clinicaltrial.gov identifier: NCT03450330)

Study DZ2017J0001 is a phase I/II, open-label, multicenter study to investigate the safety, tolerability, PK and anti-tumor activity of AZD4205 as monotherapy or in combination with osimertinib in patients with EGFR mutant (EGFRm) advanced stage non-small cell lung cancer (NSCLC). This study was completed on 3 September 2019. A total of 10 patients with EGFRm advanced NSCLC who relapsed from standard therapy were enrolled. These 10 patients were all exposed to AZD4205 monotherapy at 75 mg once daily, and among whom 8 patients were exposed to combination of AZD4205 and osimertinib after completion of AZD4205 monotherapy. AZD4205 demonstrated good tolerability as monotherapy at 75 mg once daily, and no dose limiting toxicities (DLTs) were observed during the AZD4205 monotherapy part. As of February 22 2020, the longest duration on AZD4205 was > 8.5 months in study DZ2017J0001. Blood samples were collected from all 10 patients after single dosing to assess PK of AZD4205. Data showed moderate inter-individual variability and a long $T_{1/2}$ of around 45 h, which favors to achieve sustained target inhibition. The exposure after multiple dosing showed moderate accumulation of AZD4205 concentration in plasma. Blood samples were collected from 9 patients after single dosing and 7 patients after multiple dosing to assess blood pSTAT modulation after AZD4205 monotherapy treatment. Around 60% inhibition of pSTAT1 and pSTAT5 was detected with AZD4205 single dosing, and around 80% inhibition of pSTAT1 and pSTAT5 was detected with repeat dosing. There was around 30-40% inhibition of pSTAT3 after single and multiple dosing of AZD4205. Based on nonclinical pharmacology data, clinical PK and pharmacodynamic data, 150 to 250 mg once daily is anticipated to provide sustained inhibition of pSTAT3 for clinical benefits.

Study DZ2018J0001 (clinicaltrial.gov identifier: NCT03728023)

Study DZ2018J0001 is a phase I, randomized, double blind, placebo controlled 2-parts study to assess the safety, tolerability, PK of AZD4205 following single and multiple ascending doses in healthy adult subjects, and to assess the effect of food on the PK of AZD4205. This study was completed on 20 August 2019. A total of 66 healthy female and male subjects were enrolled in this study, among who 50 patients received AZD4205 single or repeat dose. Part A enrolled subjects to receive single dose of AZD4205 at 5, 20, 50, 100 or 150 mg, and a separate cohort enrolled subjects to receive single dose of AZD4205 at 50 mg under fasted or fed condition. Part B enrolled subjects to receive repeat dose of AZD4205 at 25, 50 or 100 mg once daily for 14 days. AZD4205 was well tolerated by single or repeat dosing. No serious adverse events were observed.

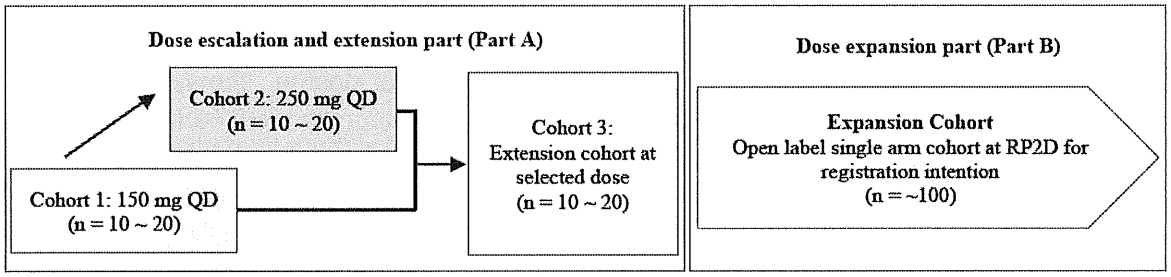
AZD4205 were well absorbed following oral administration with peak concentrations achieved within a median T_{max} of 2.5 to 8.0 hours following single-dose administration and 4 to 6 hours with repeated once daily dosing. Plasma elimination half-life of AZD4205 averaged 46.6 to 49.5 hours, which supports once daily dosing. As expected with long half-life, accumulation of about 3 folds was observed after multiple dosing. Plasma C_{max} and AUC values following single and multiple doses of AZD4205 increased in a dose-proportional manner. About 20% of total dose is excreted via unchanged AZD4205 in urine at 25, 50 and 100 mg once daily. High fat and high calorie food did not cause clinically meaningful changes on AZD4205 exposure at 50 mg single dose.

3. STUDY DESIGN AND RATIONALE

3.1 Overall study design and flow chart

This is a phase I/II, open-label, multicenter study of AZD4205 administered orally in patients with r/r PTCL to determine its safety, tolerability, PK, and anti-tumor activity. The study design allows an escalation of dose with intensive safety monitoring to ensure the safety of the patients.

Figure 1 Overall Study Flow Chart



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

3.1.1 Part A Dose escalation cohorts

Approximately a total of 40 patients will be enrolled into 2 dose escalation cohorts and receive once daily dosing of AZD4205 at 150 mg or 250 mg. The dose escalation to 250

mg will be agreed with safety review committee (SRC) based on the safety, tolerability, PK and efficacy data derived from 150 mg dose cohort.

Eligible patients will receive multiple once daily dosing of AZD4205 until disease progression, unacceptable toxicity, discontinuation criteria have met, withdrawal of consent or termination of the study by Sponsor. Each cycle of therapy will be approximately 21-day repeated dosing. Safety assessment will be conducted in every cycle. Evaluation of tumor response will be conducted based on the 2014 Lugano classification (Cheson BD et al. 2014).

Tumor tissue and blood samples will be collected from all patients who participate in this study. [redacted] but not limited to JAK/STAT mutations in tumor and blood samples, and pSTAT expression in tumor samples will be performed. If anti-tumor efficacy signals are observed, analysis will be performed to evaluate the correlation between JAK/STAT mutation and tumor response.

3.1.2 Part A Dose extension cohort

Once the maximum tolerated dose (MTD), maximum absorbable dose (MAD) or recommended phase 2 dose (RP2D) is defined based on safety, tolerability, PK, and efficacy data from dose escalation cohorts, an additional cohort of approximately 10~20 patients is planned to be enrolled in order to further explore the tolerability, PK, and anti-tumor efficacy of AZD4205 at selected dose in a single caspule dosage form. The extension cohort will also explore pSTATs modulation of blood cells by AZD4205.

3.1.3 Part B Dose expansion cohort

This part of the study is designed as an open-label single arm cohort, which is planned to enroll around 100 patients with PTCL who have relapsed after or been refractory/intolerant to ≥ 1 (but not > 3) prior treatment regimen(s). The primary obejctive of this part is to evaluate anti-tumor efficacy of AZD4205 at RP2D (CT-based ORR assessed by IRC per Lugano criteria as primary endpoint) in patients with r/r PTCL. This part will also assess the safety, tolerability, PK and anti-tumor efficacy (other endpoints) of AZD4205 at RP2D (see Section 1.2 and Figure 2). Result of this part is planned to be used for marketing application of AZD4205 in patients with r/r PTCL.

The clinical cut-off for the clinical study report (CSR) is defined as at least 6 months after confirmation of the last initial tumor response.

This part of the study is composed of an initial screening phase (up to 28 days), a single-arm treatment phase, a follow-up phase and a survival phase:

- **Screening phase**: Screening evaluations will be performed within 28 days prior to the first dose of study drug. Patients will sign the informed consent form prior to any screening evaluations. Please refer to Table 3 for details on screening procedures.
- **Treatment phase**: All patients will be treated with AZD4205 at 150 mg once daily, administered orally and will continue to be treated until disease progression, unacceptable toxicity, death, withdrawal of consent, maximum treatment duration (see

Section 5.1.4) or the study is terminated by the sponsor. A treatment cycle consists of 21 days.

- **Follow-up phase**: A follow-up should be made after 28 days (± 7 days) following the last dose of the study treatment for safety follow-up. Assessments to be performed are presented in Table 3.
- **Survival phase**: Patients will be followed up for survival via phone contact (with patient's guardian, if applicable) every 3 months after the patient's last visit until withdrawal of consent, lost to follow-up, death, or the date of data cutoff for the final analysis. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug. Subjects lost to follow up should also be recorded on the CRF. The status of ongoing, withdrawn (from the study) and "lost to follow-up" subjects at the time of an OS analysis should be obtained by the site personnel by checking the subjects notes, hospital records, contacting the subjects general practitioner and checking publicly available death registries. In the event that the subject has actively withdrawn consent to the processing of their personal data, the vital status of the subject can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

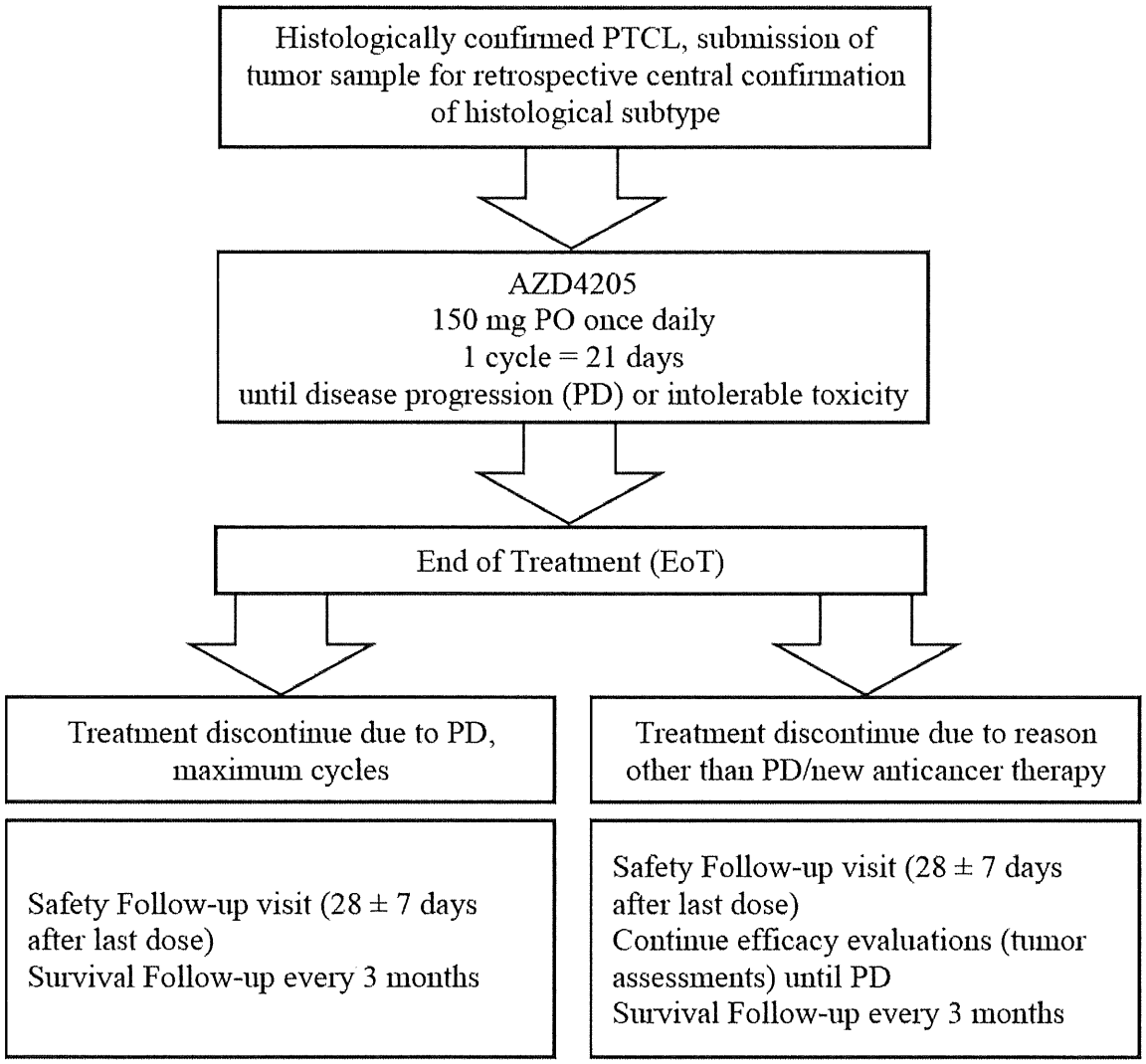
For the primary efficacy analysis, tumor response will be evaluated by an IRC based on central imaging assessment according to Lugano criteria (Cheson BD et al. 2014).

All patients should undergo contrast CT scan and bone marrow aspiration/biopsy at screening. During treatment, CT scans of the same sites as screening will be done for tumor response assessment within 7 days of Day 1 of Cycle 3, 6, 9 and then every 3 cycles until PD or withdrawal from the study. Bone marrow aspiration or biopsy is required to confirm a complete response for patients with bone marrow disease involvement at baseline (screening).

PET scan, where available, needs to be performed at screening for baseline tumor metabolism assessment. For patients with FDG-avid disease at baseline, PET should be reexamined for metabolic response assessment on Day 1 of Cycle 3, and when clinically need to confirm a complete metabolic response (CMR). Patients with confirmed CMR are not required to undergo further PET scans on study unless there is suspicion of progressive disease. If disease is not FDG-avid at baseline, PET scan is not required for efficacy assessment after study treatment initiates.

Subjects who are discontinued from study drug for any reason (i.e., AE or administrative reasons etc.) other than disease progression should not be considered withdrawn from the study. They will continue to be followed for efficacy evaluations per schedule outlined in Table 3 until subject exhibits first progression, withdrawal of consent, death, lost to follow-up, or study termination from sponsor, whichever occurs first. If subjects refuse to return for these visits or are unable to do so, every effort should be made to contact them or obtain information by telephone to determine the subject's disease status and survival.

Figure 2 Schema for dose expansion study (Part B)



Abbreviations: PTCL, peripheral T cell lymphoma; PO orally taken: EOT, end of treatment; PD, progressive disease

3.2 Rationale for conducting this study and study design

3.2.1 Rationale for conducting this study

- PTCL represents approximately 10%-25% of non-Hodgkin lymphoma and is a heterogeneous disease with broad morphological spectrum and immunophenotypic variations among patients (Gaulard P et al. 2014). For most subtypes of PTCL, the frontline treatment regimen is typically combination chemotherapy and refractory regimen is the histone deacetylase inhibitors, which often just offers limited clinical benefit (Moskowitz AJ et al. 2017). Although Brentuximab Vedotin is approved for CD30 positive ALCL, targeted therapy for the most common PTCL subtypes is still lacking. Thus, there is an unmet need for new targets and treatment options both in upfront and relapsed settings of PTCL.

- JAK kinases are key mediators of STAT activation and cytokine signaling, JAK1 mediates signaling of IL-6 and IL-10. Activated JAK kinases phosphorylate members of the STAT family of transcriptional factors and promote STAT-dependent signaling pathways. Constitutive STAT3 activation / phosphorylation has been shown to be oncogenic, driving the expression of genes promoting proliferation, survival, angiogenesis and pro-tumoral immune response.
- The critical roles of JAK and STAT proteins in hematopoietic oncology have been demonstrated in mice (Khwaja A. 2006). The activation or aberration of JAK/STAT pathway is considered as a therapeutic target for several aggressive cancers, including various solid tumors, leukemia, and lymphoma (Han JJ et al. 2018, Kucuk C et al. 2015). JAK/STAT pathway aberrations associated with poor prognosis in lymphoma has also been reported (Han JJ et al. 2018).
- Inhibition of JAK/STAT pathway by Ruxolitinib, a JAK1/JAK2 inhibitor, showed promising anti-tumor activity in patients with PTCL, especially PTCL patients with JAK/STAT pathway aberrations (Moskowitz AJ et al. 2018). Thus, inhibition of JAK/STAT pathway is an attractive therapeutic approach for patients with PTCL.
- Pre-clinical *in vitro* data showed that AZD4205 inhibited pSTAT3 (Y705) with an IC_{50} of [redacted] in HuT102 T-cell lymphoma cells harboring JAK/STAT pathway aberration. It also demonstrated effective inhibition of tumor cell proliferation by AZD4205 (GI_{50} [redacted] *In vivo* data showed that AZD4205 induced sustained pSTAT3 inhibition in lung cancer xenograft models. There was a good PK/pharmacodynamics/efficacy correlation of AZD4205 in these models.
- Clinical data from the completed study DZ2017J0001 in Australia (clinicaltrials.gov identifier: NCT03450330) demonstrated good tolerability and encouraging anti-tumor activity of AZD4205 as monotherapy at the dose of 75 mg once daily in patients with EGFR mutant advanced NSCLC. In the completed study DZ2018J0001 in US healthy volunteers (clinicaltrials.gov identifier: NCT03728023), which includes single ascending dose (SAD), food effect (FE) and multiple ascending dose cohorts (MAD), AZD4205 demonstrated dose proportional increase of drug exposure and good tolerability up to 150 mg at a single dose, and 100 mg once daily for 14 days. In the completed hADME study in the US (clinicaltrials.gov identifier: NCT04225208), data indicated that urine and fecal route contribute significantly to excretion of AZD4205 and metabolites.

3.2.2 Rationale for study design

Study design

PTCL is a relatively rare and heterogeneous disease with broad morphological spectrum and immunophenotypic variations among patients (Gaulard P et al. 2014). Most PTCL subtypes present a rather aggressive course of disease, with very limited therapeutic options. Thus, there is a huge unmet need for new targets and treatment options in PTCL.

Constitutive activation of JAK/STAT pathway is associated with poor prognosis of PTCL, and the inhibition to this pathway shows promising anti-tumor signal in some clinical

studies. AZD4205 is a potent and high-selective JAK1 inhibitor, with a favourable PK profile. Nonclinical studies showed promising anti-tumor activity of AZD4205 in T cell lymphoma, with a good PK / pharmacodynamics / efficacy correlation.

This study aims to address the safety, tolerability, PK and anti-tumor activity of AZD4205 in patients with PTCL. This study includes two parts, Part A: dose escalation and extension; Part B: dose expansion.

In Part A, patients with PTCL who relapsed from or are refractory to standard systemic therapy, or are intolerant to standard therapy, will be treated with AZD4205 at 2 different doses to evaluate safety, tolerability, PK and anti-tumor efficacy. Further extension of the cohort at selected dose is planned to be triggered with emerging safety and/or efficacy data.

The doses of this part of the study are defined based on the clinical data obtained from other completed AZD4205 clinical studies, including study DZ2017J0001 (clinicaltrials.gov identifier: NCT03450330, EGFR mutant advanced NSCLC) and study DZ2018J0001 (clinicaltrials.gov identifier: NCT03728023, healthy volunteer) and Study DZ2019J0002 (clinicaltrials.gov identifier: NCT04225208, hADME study in healthy volunteer). In study DZ2017J0001, the starting dose of AZD4205 75 mg once daily as monotherapy was well tolerated. No dose limiting toxicities (DLTs) were observed. In study DZ2018J0001, AZD4205 was well tolerated up to 150 mg (the highest dose tested) in healthy volunteers. No $\geq$ grade 3 AEs were observed. In addition, based on PK and biomarker data (pSTAT1, pSTAT3 and pSTAT5) in DZ2017J0001 study, AZD4205 150 mg once daily and above is predicted to be biologically effective for patients with PTCL. In Study DZ2019J0002, no $\geq$ grade 3 AEs were observed. With the above data and information, the doses of this study are defined as 150 mg and 250 mg once daily, respectively. Additional dose cohorts may be expanded with emerging safety and/or efficacy data.

In Part A, approximately 10 evaluable patients will be enrolled into 150 mg dose cohort to evaluate safety/tolerability, PK and anti-tumor efficacy. If the dose is well tolerated, Safety Review Committee (SRC) will review all available safety and efficacy data to decide whether to escalate the dose to 250 mg. Once the MTD, MAD or RP2D is defined based on safety, tolerability, pharmacokinetics, and efficacy data from dose escalation cohorts, approximately 10~20 additional patients are planned to be enrolled into an extension cohort and receive AZD4205 at a selected dose in a single capsule dosage form to further assess its tolerability, PK, and anti-tumor efficacy. In this extension cohort, the effect of AZD4205 on modulation of pSTATs of blood cells will also be evaluated.

In Part B, patients with r/r PTCL are planned to be enrolled into an open label single arm cohort to evaluate anti-tumor efficacy (ORR as primary endpoint) of AZD4205 at RP2D. In addition, this part of the study will also assess safety, tolerability, PK and anti-tumor efficacy (other endpoints) of AZD4205 at RP2D. Result of this part is planned to be used for marketing application of AZD4205 in patients with r/r PTCL. The sample size and design of this part will be agreed with regulatory authorities before patient enrollment.

Rationale for determination of RP2D

The RP2D was defined as 150 mg once daily per PK/PD modelling based on pre-clinical and clinical data and using pSTAT3 as the pharmacodynamics biomarker:

- pSTAT3 as pharmacodynamics biomarker

  In both the HuT102 T-cell lymphoma cell line and xenograft model, inhibition of pSTAT3 correlated with the dose-dependent exposure of AZD4205. This extent of inhibition coincided with the anti-proliferative and anti-tumor activities of AZD4205. Therefore, pSTAT3 could be used as a pharmacodynamics biomarker for AZD4205.

- Dose regimen

  In the clinical study in patients with EGFRm NSCLC (DZ2017J0001), AZD4205 at 75 mg once daily resulted in around 30% inhibition of pSTAT3 in the blood cells.

  Based on PK/pharmacodynamics modelling, 150 mg once daily and above was predicted to provide an effective concentration above all the IC_{50}s of pSTAT3 accounting for PK variability.

  In Study DZ2019J0005, preliminary efficacy (data cut-off: June 30, 2020) of AZD4205 was observed at 150 mg once daily in PTCL patients, with ORR of 42% and complete response rate (CRR) of 21%. These findings suggest the PK/PD modelling established based on data generated in HuT102 cell line and xenograft model, *ex vivo* pSTAT3 modulation in human PBMCs as well as pSTAT3 modulation in the blood cells from the patients with EGFRm NSCLC is applied for prediction of clinical efficacy.

  In addition, there was a trend showing a higher frequency and seriousness of AEs at 250 mg, compared with 150 mg. Considering long term tolerability and co-medications which need to be used for pneumocystis prophylaxis and treatment of comorbidities for patients with PTCL, 150 mg was finally selected as RP2D for the phase 2 pivotal study.

  The elimination half-life of AZD4205 is approximately 46.6 to 49.5 hours, which supports a once daily dosing regimen.

- Ethnic sensitivity

  Based on the available PK data in clinical studies, ethnic sensitivity of AZD4205 is not a concern. Therefore, the same RP2D and schedule will be applied across different regions and countries.

Efficacy assessments

In Part A, the efficacy endpoints include ORR, DoR and PFS, which will be based on local investigators' assessment according to Lugano criteria (Cheson BD et al. 2014).

In Part B pivotal study, the efficacy endpoints include ORR, DoR, CRR, PFS and TTR, which will be based on assessment by IRC per Lugano 2014. The CT-based ORR will be applied as the primary efficacy endpoint, and the rest of endpoints will be applied as the secondary endpoints. The responders will be followed up for at least 6 months after initial documented response. Tumor response will also be assessed by local investigators, and analysis will be performed to compare ORR assessed by IRC and local investigators.

[redacted]

[redacted]

4. PATIENT SELECTION AND RESTRICTIONS

Investigators should keep a record i.e., patient screening log, of patients who entered pre-study screening. Eligibility should be reviewed and documented by the investigator, or appropriately qualified delegate, prior to enrollment.

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study at the time of starting study treatment. Under no circumstances can there be exceptions to this rule, only in exceptional cases, with express permission of the sponsor. Patients who do not meet the criteria for participation in this study (screen failure) may be rescreened. Only one-time rescreening is allowed in the study. Rescreened patient should be assigned a new screening number for every screening/rescreening event.

4.1 Inclusion criteria

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

1. Provision of a signed and dated, written informed consent form prior to any study specific procedures, sampling and analyses.
    - *Patients enrolled into Part A (dose escalation and extension cohorts) must provide archived or freshly-obtained tumor samples for the exploration of genetic factors and protein expression.*
    - *In Part B expansion cohort, submission of the tumor block or unstained slides from an excisional biopsy from nodal or extra-nodal lymphoma tissue (archived or newly obtained sample) is required for retrospective central confirmation of tumor histological subtype.*
2. Aged ≥ 18 years old (for Korean ≥ 19 years old).
3. Patients must exhibit Eastern Cooperative Oncology Group (ECOG) performance status 0-2 with no deterioration over the previous 2 weeks.
4. Predicted life expectancy ≥ 12 weeks.
5. Patients must have histologically confirmed peripheral T-cell lymphoma by local pathology review according to the 2016 revision of the World Health Organization classification of lymphoid neoplasms (Swerdlow SH et al. 2016). Eligible histological subtypes are restricted to the following*:
    - PTCL-not otherwise specified (PTCL-NOS)^
    - Angioimmunoblastic T-cell lymphoma (AITL)

- Anaplastic large-cell lymphoma ALK+ (ALCL ALK+)
- Anaplastic large-cell lymphoma ALK- (ALCL ALK-)
- Enteropathy-associated T-cell lymphoma (EATL)
- Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)
- Natural killer/T-cell lymphoma (NKTCL)
- Hepatosplenic T-cell lymphoma (HSTCL)
- Subcutaneous panniculitis like Tcell lymphoma (SPTCL)

** In part B, histological subtypes will be confirmed by retrospective central pathology review.*

[redacted]

6. Patients must have measurable disease according to the 2014 Lugano classification, which is defined as below.

   Lymphomatous nodes, nodal masses, or other lymphomatous lesions are measurable in two diameters (longest diameter [LDi] and shortest diameter perpendicular to the LDi [SDi]) on CT scans, and also with LDi as below.

   - A measurable node must have an LDi greater than 1.5 cm.
   - A measurable extranodal lesion should have an LDi greater than 1.0 cm.

7. Patients must have progressed on or are refractory to standard systemic therapy, or patients were intolerant to standard systemic therapy. Patients should be transplant-ineligible upon their entries to this study.

   In part B, eligible patients must have relapsed after or been refractory/intolerant to ≥ 1 (but not > 3) prior systemic therapy(ies) for PTCL and now require further treatment. In patients with CD30 positive ALCL, the prior systemic treatment should include CD30-targeting therapy (brentuximab vedotin) if the therapy is approved and available as standard therapy, unless in the judgment of the investigator such treatment was otherwise contraindicated.

8. Adequate bone marrow reserve and organ system functions, as outlined below:

   - Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L (≥ 0.5 × 10^9/L if documented bone marrow involvement with lymphoma) independent of growth factor support within 7 days of study entry.
   - Platelets ≥ 100 × 10^9/L (or ≥ 50 × 10^9/L if documented bone marrow involvement with lymphoma) independent of growth factor support or transfusion within 7 days of study entry.
   - Hemoglobin ≥ 8 g/dL
   - Total bilirubin ≤ 1.5 × ULN if no liver involvement or ≤ 3 × ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver involvement.

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN, or ≤ 5 × ULN if with document hepatic involvement with lymphoma.
- Creatinine ≤ 1.5 × ULN, OR calculated or measured creatinine clearance ≥ 50 mL/min as calculated by the Cockcroft-Gault method, or 24-hour measured urine creatinine clearance ≥ 50 mL/min.

9. LVEF ≥ 55% assessed by ECHO or MUGA.
10. Patients should have the ability and willingness to comply with the study and follow up.
11. Male patients with female partners of child-bearing potential should be willing to use barrier contraceptives (i.e., by use of condoms), during their participation in this study and for 6 months following the last dose of the study drug.

    Male patients must refrain from donating sperm during their participation in the study and at least for 6 months after the last treatment. If male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.
12. Female patients should be using adequate contraceptive measures while on study drug and for 3 months following the last dose of study drug. Acceptable methods of contraception include total and true sexual abstinence, tubal ligation, hormonal contraceptives that are not prone to drug-drug interactions [IUS Levonorgestrel Intra Uterine System (Mirena), Medroxyprogesterone injections (Depo-Provera)], copper-banded intra-uterine devices and vasectomised partner. All hormonal methods of contraception (with the exception of total abstinence) should be used in combination with the use of a condom by their male sexual partner for intercourse. Female patients should not be breast-feeding and must have a negative pregnancy test prior to start of dosing if of childbearing potential or must have evidence of non-childbearing potential by fulfilling one of the following criteria at screening:
    - Post-menopausal women defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatment.
    - Women under 50 years old would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution.
    - Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, but not tubal ligation.

4.2 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

1. Intervention with any of the following:
    - Any investigational agents or study drugs from a previous clinical study within 30 days of the first dose of study treatment.

- Any cytotoxic chemotherapy from a previous treatment regimen within 21 days of the first dose of study treatment.
- Prior HDAC inhibitors (including romidepsin, belinostat and chidamide) or pralatrexate therapy within one week of the start of the study treatment.
- Corticosteroids at dosages equivalent to prednisone > 15 mg/day within 7 days of the start of the study treatment.
- Major surgery procedure (excluding placement of vascular access), or significant traumatic injury within 4 weeks of the first dose of study treatment, or have an anticipated need for major surgery during the study.
- Prior therapeutic anticancer antibodies (including brentuximab vedotin) within 4 weeks, other radio- or toxin-immunoconjugates within 10 weeks, radiation therapy within 3 weeks.
- Patient has undergone an allogeneic stem cell transplant. Patient had autologous stem cell transplant within 6 months.
- Prior treatment with a JAK or STAT3 inhibitor.
- Prior treatment with any onco-immunotherapy in 28 days prior to first dosing of AZD4205 (e.g. immune checkpoint inhibitors PD-1, PD-L1, CTLA-4). Other novel agents within clinical trials need to be evaluated by both investigator and Study Physician before enrollment).
- Live vaccines within 28 days prior to first dose.
- Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose) vitamin K antagonists, anti-platelet agents or anticoagulated agents.
- Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose) medications or herbal supplements known to be Potent inhibitors or inducers of CYP3A or sensitive substrates of BCRP or P-gp with narrow therapeutic index (see Appendix II).

2. Any unresolved toxicities from prior therapy, greater than Common Terminology Criteria for Adverse Events (CTCAE v 5.0) Grade 1 at the time of starting study treatment with the exception of alopecia.
3. Central nervous system or leptomeningeal lymphoma.
4. Patients with severely decreased lung function (i.e. any parameter of FEV1, and DLCO < 60% of predicted value). Past medical history of pneumonitis, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.
5. Patients with disease condition which requires the treatment of immunosuppressants, biologics, or NSAIDs (non-steroid anti-inflammatory drugs).
6. Active infections including:

- History of known latent or active tuberculosis (TB), e.g. signs of active or latent TB on PPD test or chest X-ray/CT, skin test showing an induration of >10 mm or more, or positive results of screening tests according to local recommendations.
- Known infection with human immunodeficiency virus (HIV), or serologic status reflecting active hepatitis B or hepatitis C infection as follows:

	Inclusion	**Exclusion**
HIV antibody	Negative	Positive
HCV antibody	Negative	Positive
HBV	Both HBsAg and HBcAb are negative	Either HBsAg or HBcAb is positive

- Active viral infections (i.e. zoster) other than hepatitis B or C.
- Infections requiring oral or intravenous antimicrobial therapy or interferon.
- Bacterial infections including pneumonia within 30 days.

7. Any of the following cardiac criteria:
   - Congestive heart failure (CHF) per New York Heart Association (NYHA) classification > Class II (see Appendix I).
   - Clinically significant valvular diseases, hypertrophic or constrictive cardiomyopathy.
   - Any clinically significant abnormalities in rhythm, conduction or morphology of resting ECG, e.g., complete left bundle branch block, third degree heart block, and second-degree heart block, PR interval > 250 msec.
   - Cardiac ventricular arrhythmias requiring anti-arrhythmic therapy.
   - Acute Myocardial Infarction (AMI) within 6 months prior to starting treatment, unstable angina or new-onset angina.
   - Patients with heart transplant.
   - Mean resting corrected QTcF interval (QT_C) > 450 ms on screening triplicate electrocardiogram (ECG).
   - Patients with factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalaemia, congenital long QT syndrome, any concomitant medication known to prolong the QT interval (Appendix II)) or family history of long QT interval syndrome or unexplained sudden death under 40 years of age in first degree relatives).
   - Patients with previous/current thrombotic diseases such as pulmonary embolism, and deep venous thrombosis.
8. Another malignancy within 5 years prior to enrollment with the exception of adequately treated in-situ carcinoma of the cervix, uterus, basal or squamous cell carcinoma or non-melanomatous skin cancer.

9. Refractory nausea and vomiting if not controlled by supportive therapy, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of AZD4205.
10. Women who are breast feeding.
11. History of hypersensitivity to active or inactive excipients of AZD4205 or drugs with a similar chemical structure or class
12. As judged by the investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension or active bleeding diatheses. Screening for chronic conditions is not required.
13. Concurrent conditions that in the investigator's opinion would jeopardize compliance with the protocol.
14. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.
15. Involvement in the planning and conduct of the study (applies to Sponsor staff or staff at the study site).

4.3 Restrictions

4.3.1 Concomitant treatments

Information on any treatment within 4 weeks prior to starting of study treatment and all concomitant treatments given during the study along with reasons for the treatment will be recorded in the Case Report Form (CRF).

All patients must avoid concomitant use of medications, herbal supplements and/or ingestions of foods with known potent inducer/inhibitory effects on CYP3A activity whenever feasible. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period after the last dose of AZD4205. Guidance on medications to avoid, medications that require close monitoring and on washout periods is given in Appendix II.

Patients taking concomitant medications whose disposition is dependent upon Breast Cancer Resistance Protein (BCRP) and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving study treatment. Patients may take cholesterol-lowering drugs if considered by the investigator to be medically indicated. Patients taking rosuvastatin should have creatinine phosphokinase levels monitored due to BCRP-mediated increase in exposure. If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.

In vitro, AZD4205 demonstrated inhibition of kidney transporters including OCT2, MATE1 and MATE2-K, a clinically relevant drug-drug interaction (DDI) via inhibition of these transporters could not be discounted. Active secretion via kidney transporters are highly involved for metformin elimination, thus inhibition of these transporters has the

potential to interfere with the transport of metformin and ultimately affect both plasma and intracellular concentrations of metformin. Lactic acidosis, a rare but serious complication, can occur due to metformin accumulation (Please refer to Appendix II. GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS for examples of drugs that are sensitive OCT2, MATE1 and MATE2-K substrates with narrow therapeutic index that fall into this category).

Patients must avoid live vaccines during the study.

Short-term corticosteroids at dosages equivalent to prednisone $\leq$ 15 mg/day could be given to patients with B symptoms.

Given the mechanism of JAK inhibitors, the hepatic disorders are not considered as a significant risk for AZD4205, but cautions should be taken when acetaminophen or drugs containing acetaminophen are administered with AZD4205, and high dose/overdose of acetaminophen (propacetamol) or drugs containing acetaminophen (propacetamol) should be prohibited.

4.3.2 Supportive care and prophylactical therapy

Patients may receive any medication that is clinically indicated for treatment of adverse events, unless specifically excluded. All concomitant medications should be captured on the electronic CRF (eCRF).

1. Other anticancer agents, investigational agents and radiotherapy should not be given while the patient is receiving study treatment. The patient may be allowed to take localized palliative radiotherapy for pain control if it has been confirmed that there is no disease progression on the local lesion.
2. Blood transfusions are allowed at any time during the study treatment phase.
3. Granulocyte colony stimulating factors should not be used prophylactically during Cycle 1. Use of prophylactic colony stimulating factors may be considered after Cycle 1 following discussion with the Sponsor Study Physician.
4. Supportive care and other medications that are considered necessary for the patient's well-being, may be given at the discretion of the investigator.
5. Serious infection is an identified risk for the approved JAK inhibitors, and patients with relapsed or refractory PTCL are at a high risk of opportunistic infection. Pneumocystis pneumonia has been reported in the clinical study with AZD4205. Therefore, **for all patients during the treatment, pneumocystis prophylaxis is required**. Please follow institutional guidelines or European Conference on Infections in Leukemia (ECIL) guideline (Maertens J et al. 2016, Cordonnier C et al. 2016).
6. For patients with history of cytomegalovirus (CMV) infection that required treatment, prophylactic treatment and monitoring for reactivation via serology or viral load detection per institutional guidelines is recommended.
7. For patients with tumor response during the study, it is not recommended to subsequently receive bone marrow transplantation, e.g. autologous or allogenic stem cell transplantation (SCT). If patients require SCT, AZD4205 should be discontinued

after discussion with sponsor study physician, and tumor response assessment should still be performed as scheduled after discontinuation.

5. STUDY TREATMENT AND CONDUCT

5.1 Study Treatment

Supply, Packaging and Labelling of AZD4205

AZD4205 drug substance and drug product to be used for this clinical study are manufactured in accordance with Good Manufacturing Practice (GMP).

AZD4205 will be given orally once daily as capsule(s). Doses should be taken approximately 24 hours apart at the same time point each day. For the purpose of planning, each 3 week period (21 days) will be defined as a Cycle.

Capsules will be packed in HDPE bottles with child-resistant closures. One or more bottles of AZD4205 will be dispensed at each dispensing visit depending on the dose. Bottles will be dispensed to subjects in the Sponsor packing provided. The packaging includes bottles, caps and a label. Bottle tampers should not be broken prior to dispensing study drug to a patient.

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

The label will include the Name of the Sponsor, Protocol Number, For Clinical trial use only and/or any other market specific requirements.

AZD4205 capsules must be stored at 2-30 °C (1-30 ℃ in Korea) in the original container(s), unless being prepared for administration.

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the pack specifies the appropriate storage.

Drug administration

Patients will receive repeat dosing of AZD4205 at 150 mg or 250 mg once daily. Each cycle of therapy will be approximately 21 day repeated dosing. Patients may continue to receive AZD4205 at the discretion of the investigator until disease progression per Lugano criteria, unacceptable toxicity, discontinuation criteria have met, withdrawal of consent or termination of the study by Sponsor.

AZD4205 capsule(s) can be taken whole with water, with or without regard to food. However, subjects will be required to fast (water only) for at least 8 hours prior to the collection of a serum chemistry sample as per the study plan (see Table 2 and Table 3).

If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the dose time, the missed dose should not be taken, and the patient should be instructed to take the next dose at the next scheduled

time. If a patient vomits after taking AZD4205, he/she should not make up for this dose, but should take the next scheduled dose.

5.1.1 Dose escalation and extension part (Part A)

The dose escalation part (Part A) contains two ascending dose cohorts. Each cohort is planned to enroll 10~20 patients with r/r PTCL who will receive AZD4205 at 150 mg or 250 mg once daily dosing. The decision of dose escalation to AZD4205 250 mg level is made by the safety review committee (SRC) based on all the available safety, tolerability and PK data of the starting dose (150 mg). After the RP2D is defined, an extension cohort will enroll ~10-20 patients to evaluate single capsule dosage formulation at RP2D (see Figure 1).

5.1.1.1 Dose escalation cohorts

The first 10 patients will receive AZD4205 at the dose of 150 mg once daily. This dose was defined based on the clinical data from other completed AZD4205 studies, including study DZ2017J0001 (EGFR mutant advanced NSCLC), study DZ2018J0001 (healthy volunteers) and study DZ2019J0002 (healthy volunteers). The 150 mg dose is predicted to be biologically effective for patients with PTCL, especially patients with JAK/STAT pathway aberrations. Once there are 10 evaluable patients who complete the safety assessment in the first repeat dosing cycle in each cohort, a decision will be made by SRC based on safety/tolerability, PK and efficacy data if additional patients need to be enrolled into the same dose cohort or dose escalation to 250 mg.

Patients who discontinue treatment early due to disease progression or withdrawal will be asked to complete all end-of-treatment safety evaluations as described in the protocol. Patients who take less than 80% of planned doses within the first dosing cycle are considered not evaluable and will be replaced, unless the incompletion of dose is caused by dose-limiting toxicity (DLT) like event. Final evaluability should be determined by SRC.

Safety Review Committee (SRC)

The SRC will evaluate the safety, tolerability, efficacy and PK of AZD4205 to decide expansion of a dose cohort or dose escalation to the next level.

The SRC will consist of:

- Sponsor Study Physician
- Global coordinating investigator and national coordinating investigator or their delegate
- Sponsor Safety Physician.

Other principal investigators, Medical Director, Clinical Operation Director, Clinical Pharmacology Scientist, Study Statistician, Patient Safety Scientist, and Study Leader, further internal or external experts may be consulted by the SRC as necessary.

Once there are at least 10 evaluable patients at a dose level, the SRC will review and assess all available safety and efficacy data from the cohort together with available PK to make a

decision on expansion of a dose cohort or dose escalation to the next dose level. Any dose interruptions and reductions will be taken into account.

The decision may be to:

- Expand the cohort to a maximum number of patients.
- Dose escalation to next dose level
- De-escalate the dose to a lower dose level.
- Consider alternative dosing frequencies or intermittent dosing schedules.
- Trigger additional dose cohort(s) based on the safety/tolerability, PK and anti-tumor efficacy data.

When there are other patients that are ongoing at the time of this review, the SRC may decide to defer their decision until these further patients become evaluable.

Any patient started on treatment in error, as he/she failed to comply with all of the selection criteria but meets the criteria of an evaluable patient, will be reviewed on a case by case basis by the SRC to determine if the patient should be included or excluded for decision.

Definition of DLT-like event

Any toxicity not attributable to the disease or disease-related processes will be considered a DLT-like event if it occurs during Cycle 1 (first 21 days of repeated dosing of AZD4205) in dose escalation cohorts. DLT-like events will be defined as the following:

- Hematological toxicity including:
  - CTCAE (version 5) Grade 4 or above present for more than 4 days
  - Febrile neutropenia
- Non-hematologic toxicity including:
  - Grade 3 or 4 non-hematologic toxicity (excluding alopecia), that is dose limiting in the judgment of the investigators and the Medical Monitor/Study Physician

    Grade 3 or 4 laboratory abnormalities which are not considered clinically significant and which resolve within 48 hours, will not be considered as a DLT
  - An increase in AST or ALT $\geq$ 3×ULN and total bilirubin $\geq$ 2×ULN where no other reason other than investigational treatment can be found to explain the combination of increase
  - Confirmed QTc prolongation (> 500 msec absolute or > 60 msec above baseline)
  - Decrease in lung function: either DLCO or FEV1% decrease to $\geq$ CTCAE Grade 3
  - LVEF decrease to < 40%; or LVEF [40 - 54%] and LVEF $\geq$ 10% decrease from baseline; or any symptomatic LVEF decrease.
- Any other toxicity that:
  - is greater than baseline, is clinically significant and/or unacceptable, and is judged

to be a DLT-like event by the SRC

- that is a protocol defined stopping criteria (i.e. confirmed pneumonitis or life-threatening arrthymia)
- prevents completion of at least 80% of planned doses

Dose escalation scheme

Once there are 10 evaluable patients in the initial dose cohort (i.e. completing > 80% of the planned dose in Cycle 1, or DLT-like event preventing the dose completion), the SRC will review all available safety/tolerability, PK and efficacy data in 150 mg dose cohort. If ≤ 30% of patients have DLT-like event, the dose level of AZD4205 may be escalated to 250 mg once daily. If DLT-like events are observed in > 30% of patients and efficacy signal is observed, it is recommended to continue enrolling another 10 patients in the original dose cohort (150 mg) to further assess the safety, tolerability and anti-tumor efficacy. If > 30% of patients have DLT-like event and no efficacy signal is observed, further enrollment of additional patients would be ceased. In addition, all drug interruptions and dose reductions will be taken into consideration for the decision of dose escalation by SRC.

5.1.1.2 Dose extension cohort

Once the MTD, MAD or RP2D is defined based on safety, tolerability, PK, and efficacy data of dose escalation part, a cohort of around 10~20 patients with r/r PTCL will be enrolled to evaluate single capsule dosage formulation at the selected dose.

5.1.2 Phase 2 dose expansion cohort

Once the RP2D is determined, an additional cohort of patients with r/r PTCL will be enrolled to further assess the efficacy and tolerability of AZD4205. Approximately 100 patients with r/r PTCL are planned to be enrolled, while as the result of this part is planned to support an NDA submission for AZD4205, the sample size will be discussed and agreed with regulatory authorities before initiation of enrollment. Patients will receive AZD4205 treatment until disease progression, unacceptable toxicity, discontinuation criteria have met, withdrawal of consent or termination of the study by Sponsor.

Stopping criteria for dose expansion cohort (Part B)

In Phase 2 dose expansion cohort (Part B), around 100 patients with r/r PTCL are planned to be enrolled continuously and receive AZD4205 at 150 mg once daily. TEAE related discontinuation or death will be continuously monitored. After ≥ 20 patients are enrolled and once the rate of TEAE related discontinuation or death reaches ≥ 19.7%, an ad-hoc SRC meeting will be triggered to review all available safety, tolerability and efficacy data of Part B. In the case of treatment-related death occurred (≥ 1), the study accrual will be suspended and SRC meeting will be triggered. The decision of SRC may be to:

- Make decisions on the patient recruitment plan, e.g. enrollment suspension and resumption.
- Adjust the risk management plan for the expansion cohort (Part B)
- Re-evaluate the risk-benefit balance

The criteria of 19.7% is calculated based an algorithm close to Bayesian Optimal Interval (BOIN) design (Liu S et al. 2015). We will set our target rate as 15% and un-acceptable rate as 25%. The boundary is calculated similar to λ_d in BOIN design. The un-acceptable rate of 25% is set based on TEAE leading to dose discontinuation rate in pivotal trials of approved drugs for r/r PTCL, which ranges from 19 to 23% (Coiffier B et al, 2012; O'Connor OA et al. 2011; O'Connor OA et al, 2015). While target rate is similar to our current observed TEAE leading to dose discontinuation rate of 13.9% (Data from Part A of DZ2019J0005 study as of September 11, 2020).

5.1.3 Dose modifications

5.1.3.1 Toxicity management and dose modifications to AZD4205

If a patient has a treatment emergent adverse event (TEAE) at least possibly related to AZD4205, then dose interruptions/holds with possible modifications as described in Table 1 should be implemented. Deviations from these guidelines may occur based on the clinical judgment of the investigator with notification to the Sponsor. For managing toxicity related to the eye, refer Appendix VII.

Table 1 Dose Interruptions/Modifications for Toxicities Observed in the Study

Category	Toxicities needing immediate interruption	Dose modification plan
Hematological toxicity	ANC < 0.5×10^9/L	Immediate interruption of AZD4205 Once toxicity has resolved to recovery to ≤ Grade 2 or baseline within 14 days of onset: ▪ Resume at the same dose for the 1st occurrence of the event ▪ Resume at the reduced dose for the 2nd occurrence of the event ▪ Permanent discontinue for the 3rd occurrence of the event
	Platelet count < 25×10^9/L	Immediate interruption of AZD4205 Once toxicity has resolved to recovery to ≤ Grade 2 or baseline within 21 days of onset: ▪ Resume at the same dose for the 1st occurrence of the event ▪ Resume at the reduced dose for the 2nd occurrence of the event ▪ Permanent discontinue for the 3rd occurrence of the event
	Grade 3 febrile neutropenia	Immediate interruption of AZD4205 Once toxicity has resolved to recovery to ≤ Grade 2 or baseline within 14 days of onset: ▪ Resume at the reduced dose for the 1st occurrence of the event, unless the toxicity can be safely and reliably controlled to ≤ Grade 2 or baseline with appropriate treatment. (dose may restart at 150 mg once daily after reaching an agreement with the sponsor). ▪ If the same non-hematological toxicity requiring dose interruption occurs again, AZD4205 should be permanently discontinued.
	Grade 3 thrombocytopenia with significant bleeding	Permanent discontinuation
	Other Grade 4 or unmanageable hematological toxicity(ies)	Immediate interruption of AZD4205

		Once toxicity has resolved to recovery to ≤ Grade 2 or baseline within 14 days of onset: ▪ Resume at the same dose for the 1st occurrence of the event ▪ Resume at the reduced dose for the 2nd occurrence of the event ▪ Permanent discontinue for the 3rd occurrence of the event
Non-hematological toxicity	QTcF > 500 ms absolute or > 60 ms increase from baseline	Permanent discontinuation
	QT prolongation (QTcF > 450 ms) with signs/symptoms of life-threatening arrhythmia	Permanent discontinuation
	Confirmed drug-induced pneumonitis (any grade, see Figure 3)	Permanent discontinuation
	Grade 4 non-hematological toxicity	Permanent discontinuation
	Grade 3 Herpes Zoster	Immediate interruption of AZD4205 Once toxicity has resolved to recovery to ≤ Grade 2 or baseline within 21 days of onset: ▪ Resume at the same dose for the 1st occurrence of the event ▪ Resume at the reduced dose for the 2nd occurrence of the event ▪ Permanent discontinue for the 3rd occurrence of the event
	Other Grade 3 or unmanageable non-hematological toxicity(ies)	Immediate interruption of AZD4205 Once toxicity has resolved to recovery to ≤ Grade 2 or baseline within 14 days of onset: ▪ Resume at the reduced dose for the 1st occurrence of the event, unless the toxicity can be safely and reliably controlled to ≤ Grade 2 or baseline with appropriate treatment, (dose may restart at 150 mg once daily after reaching an agreement with the sponsor). ▪ If the same non-hematological toxicity requiring dose interruption occurs again, AZD4205 should be permanently discontinued.

The reduced dose level of AZD4205 refers to 75 mg once daily. Patient should discontinue the study treatment, if he/she is already at the reduced dose level (75 mg) and requiring a further dose reduction due to toxicity according to the modification plan (as defined in Table 1).

If medically appropriate, Grade 4 abnormalities of hematology parameters which are considered to be of clinical concern may be repeated/confirmed within 7 days and followed up as appropriate. Supportive care such as transfusion and/or growth factor could be given per institutional guideline.

Supportive care for the management of the toxicities may be given to the patients as required in accordance with local practice/guidelines. Patients should permanently discontinue the study treatment, if the toxicities leading to interruption do not recover to ≤ Grade 2 or baseline within the maximum duration of dose interruption defined in Table 1. Patients with toxicities leading to dose discontinuation should be followed up until Grade 1 or baseline. Deviations from above guidelines may occur based on the clinical judgment of the Investigator with reaching agreement with the Medical Monitor/Sponsor.

5.1.3.2 Assessment timings if dosing is interrupted

If a patient misses any doses of AZD4205 during Cycle 1 and Cycle 2, please contact the Medical monitor and Study Physician for advice regarding the evaluability of the patient and appropriate timing of the PK assessments. All other assessments, including laboratory safety assessments, vital signs and response assessment should continue to be performed as per study plan, relative to the baseline assessments.

5.1.4 Duration of therapy

Patients shall continue with the study treatment until the 2014 Lugano classification defined progression, a satisfying response for more than 1 year, or other treatment discontinuation criteria are met or withdrawal of consent. A satisfying response refers to a CR or a PR with stable residual disease since the first documented CR or the first documented PR with stable residual disease per investigator's assessment. However, if the patient still benefits from longer treatment at the discretion of the investigator, even the aforementioned criterion is met, the patient may continue on treatment and the maximum treatment duration should be within two years (approximately 35 cycles). Under the circumstances that the participant is still in need of the study treatment beyond two years after a thorough assessment by the investigator, the medical monitor/study physician shall be consulted.

If the study treatment is discontinued for reasons other than disease progression, the patient must continue response assessments until disease progression, death, withdrawn of consent or study termination by sponsor.

5.1.5 Treatment compliance and accountability

The investigational product should only be used as directed in this protocol. Details of treatment with investigational product for each patient will be recorded in the CRF.

Patients should return all unused medication and empty containers to the investigator. The study personnel at the investigational site will account for all drugs dispensed and returned. Unless otherwise authorized by sponsor, all investigational product supplies unallocated or unused by the patients must be destroyed by procedures approved by sponsor or returned to sponsor or its designee.

5.2 Benefit/risk and ethical assessment

5.2.1 Potential benefits

The critical roles of JAK and STAT proteins in hematopoietic oncology have been clearly demonstrated in mice (Khwaja A. 2006) and the activation or aberration of JAK/STAT pathway is considered as a therapeutic target for several aggressive cancers, including NSCLC and PTCL (Kim SM et al. 2012, Han JJ et al. 2018, Kucuk C et al. 2015, Moskowitz AJ et al. 2018). JAK/STAT pathway aberrations associated with poor prognosis in lung cancer and lymphoma has also been reported (Gao SP et al. 2008, Song L et al. 2011, Han JJ et al. 2018). Inhibition of JAK/STAT pathway by Ruxolitinib, a JAK1/JAK2 inhibitor, showed promising anti-tumor activity in patients with PTCL, especially PTCL patients with JAK/STAT pathway aberrations (Moskowitz AJ et al. 2018). Thus, inhibition of JAK/STAT pathway is an attractive therapeutic approach for patients with PTCL.

Pre-clinical *in vitro* data showed that AZD4205 inhibited pSTAT3 (Y705) with an IC_{50} of [redacted] in HuT102 T-cell lymphoma cells harboring JAK/STAT pathway aberration. It also demonstrated effective inhibition of tumor cell proliferation by AZD4205 (GI_{50} [redacted] *In vivo* data showed that AZD4205 induced sustained pSTAT3 inhibition in lung cancer xenograft models. There was a good PK/PD/efficacy correlation of AZD4205 in these models.

AZD4205 is selective for JAK1 among JAK family with greater than 200-fold selectivity over JAK2. It would expect to spare side effect from JAK2 and potentially deliver efficacy benefit to patients.

5.2.2 Potential risks

Non-clinical toxicity studies of AZD4205 in rats and dogs and safety pharmacology experiments have been summarized in Section 2.3 of this protocol, which may indicate the potential adverse effects of AZD4205 in human. Further detailed information of non-clinical toxicity findings is available in the Investigator Brochure. The monitoring and management of the potential adverse effects of using AZD4205 is discussed below.

Cardiovascular effects

Patients who have unstable cardiac conditions and risk factors for QT prolongations will be excluded from participation in this study (detailed exclusion criteria are listed in Section 4.2). Concomitant use of regular medications that may prolong the QT interval will be restricted whenever feasible (See Appendix II), but patients may receive any medication that is clinically indicated for the treatment of AEs. Electrolyte and vital sign assessments, including pulse rate and blood pressure, will be monitored regularly throughout the study (See Section 6.1). Twelve lead ECG will be conducted throughout the study to monitor any

change of QT interval. Confirmed QTc prolongation (> 500 msec absolute or > 60 msec above baseline) is the dose interruption criteria (See Section 6.4.3). The investigator or designated physician will review each ECG prior to discharge from the clinic and may refer to a local cardiologist if appropriate for immediate management of the patients. A paper copy should be filed in the patient's medical records. 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. An Echocardiogram or MUGA scan to assess LVEF will be performed at screening prior to first dose of AZD4205 to evaluate any pre-existing cardiac abnormality, followed by Cycle 3 Day 1, and then every 12 weeks, and wherever and whenever necessary as clinically indicated throughout the study. An asymptomatic LVEF decrease to < 40% or LVEF [40-54%] and LVEF decrease ≥ 10% from baseline or any symptomatic LVEF decrease are the dose interruption criteria (See Section 6.4.5 and Appendix VII). Both high sensitive troponin T testing and NT-pro BNP will be performed at screening, baseline and each subsequent cycle.

In addition, thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT) and arterial thrombosis have occurred in patients treated with other approved JAK inhibitors (e.g. tofacitinib, baricitinib, and upadacitinib). The mechanism of these thrombosis remains unclear. Patients with previous/current thrombotic diseases such as PE and DVT will be excluded from participating in this study.

Respiratory effects

Patients with previous medical history of ILD, drug induced ILD, radiation induced pneumonitis in need of steroid treatment, or any evidence of clinically active ILD will be excluded from participation in this study.

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of interstitial lung disease, an interruption in study treatment dosing is recommended, and the Sponsor study team should be informed. A questionnaire regarding the results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters, bronchoscopy with biopsy as needed) will be sent to investigators. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of drug-induced pneumonitis should be considered, and study treatment permanently discontinued. In the absence of a diagnosis of drug-induced pneumonitis study treatment may be restarted following consultation with Sponsor Study Physician.

Hematopoietic effects

Patients with inadequate bone marrow reserve as demonstrated by any of the following laboratory values (absolute neutrophil count $<1.5\times10^9$/L, or $< 0.5\times10^9$/L if related to lymphoma; platelet count $< 100\times10^9$/L or $< 50\times10^9$/L if related to lymphoma; hemoglobin < 8 g/dL) will be excluded from the study. Hematological parameters will be monitored

prior to administration of the first dose, weekly during the first cycles of multiple dosing, at day 1 of each subsequent cycle, and at discontinuation.

Liver effects

Patients with any evidence of severe or uncontrolled systemic liver disease, including those with known hepatitis B, hepatitis C, or abnormal liver enzymes (defined as AST or ALT > 2.5×ULN, total bilirubin > 1.5×ULN if no evidence of liver involvement; AST or ALT > 5×ULN, total bilirubin > 3×ULN in the presence of liver involvement) at screening are excluded from participating in the study. During the study, liver function tests will be monitored regularly and recorded at discontinuation. Patients' laboratory results will be assessed against FDA's Draft Guidance for Drug Induced Liver Injury (FDA guidance 2009), with the process described in detail in in Appendix III. HY's Law.

GI tract effects

Patients with refractory nausea, vomiting and chronic gastrointestinal diseases are excluded from participating in this study. Investigators will also be advised to follow the general toxicity management guidelines regarding dose interruption and reduction as detailed in Sections 5.1.3.1.

Reproductive organ effects

No reproductive toxicology or teratogenicity studies have been conducted with AZD4205 to date, although the male and female reproductive tracts have been assessed as part of the 1-month toxicology studies. Therefore women of child bearing potential and all men will be required to use adequate contraceptive measures during the study and for an appropriate period thereafter (as described in Section 4.1). Women of child bearing potential must have a negative pregnancy test prior to first dose of study treatment. Women who are breast feeding will be excluded from participating in the study. Male patients will be advised to arrange for the freezing of sperm samples prior to the start of the study should they wish to father children, and not to donate sperm until 6 months after discontinuation of study treatment.

Infections

Serious infections including opportunistic infections leading to hospitalization or death have been reported in patients receiving approved JAK inhibitors (e.g. ruxolitinib, tofacitinib and baricitinib). Given the fact that patients with lymphoproliferative disorders (e.g. lymphoma) are at a high risk for Pneumocystis carinii pneumonia (PCP) infection, prophylaxis for PCP is mandatory for all patients who participate in this study. In addition, monitoring and evaluation of patients with fever and infections should be performed, and appropriate treatment should be given during the study.

5.2.3 Overall benefit-risk and ethical assessment

For PTCL patients who have progressed on or are refractory/intolerant to standard treatment, the prognosis is very poor as there is no effective treatment available. This study aims to evaluate a JAK1 inhibitor, AZD4205, which potentially provides benefit to this

population with high unmet medical need, as JAK/STAT pathway has been documented to be associated with disease biology. In addition, the selectivity profile of AZD4205 against other JAK family members might provide a better tolerability profiles in clinic. Moreover, the longer half-life of AZD4205, compared with other JAK inhibitors, could potentially achieve longer duration of inhibition of JAK/STAT pathway, and thus drives better clinical activity.

The starting dose of AZD4205 is selected based on non-clinical toxicity findings as well as clinical data derived from the completed study of AZD4205 in EGFRm advanced NSCLC in Australia. The selected doses of 150 mg and 250 mg once daily are predicted to achieve biologically effective exposure and thus potentially derive clinical benefit to patients with PTCL.

Preliminary safety data at 150 mg and 250 mg suggests AZD4205 was tolerated at both doses. The most common ≥ grade 3 drug related TEAEs (defined as incidence rate ≥ 5%) included thrombocytopenia, neutropenia and pneumonia. The majority of TEAEs were manageable and reversible. These findings were consistent with the predicted safety risks of AZD4205. The current safety monitoring and management plan in Part A could identify these safety risks, and thus will be applied in the pivotal study (Part B).

Therefore, the benefit/risk assessment for this phase I/II study appears to be acceptable.

5.3 Discontinuation of investigational product and withdrawal from study

If study treatments are discontinued for reasons other than disease progression, the patient must continue response assessments until disease progression, death, withdrawn of consent or study termination by sponsor.

5.3.1 Procedures for discontinuation of a patient from investigational product

Patients may be discontinued from investigational product in the following situations:

- Patient decision. The patient is at any time free to withdraw his/her participation in the study, without prejudice.
- Adverse events (see Table 1).
- Initiation of further line(s) of anti-cancer treatment (including bone marrow transplantation).
- Severe non-compliance to this protocol as judged by the investigator and/or Study Team.
- Disease progression as per 2014 Lugano classification, unless, in the opinion of the investigator, the patient is still deriving clinical benefit.
- Patients incorrectly initiated on investigational product (Section 5.3.2).
- Patient achieved a satisfying response confirmed for 1 year by PET or CT assessment (Section 5.1.4).
- Treatment duration reaching 2 years (approximately 35 cycles) (Section 5.1.4).

- Pregnancy.

Once study medication is permanently discontinued it cannot be restarted.

Any patient who discontinues study treatment for reasons other than disease progression should have response assessment performed as scheduled in the protocol until disease progression is documented or death occurs, unless consent is withdrawn. Study procedure related SAEs and anti-cancer treatment must be captured until the patient no longer has response assessments (disease progression or permanent withdrawal from the study).

After the final database lock, there may be some patients remaining on study treatment. For these patients, sponsor will collect information during the treatment period and for 28 days (± 7 days) after last dose on SAEs, death (including those due to disease progression), discontinuation due to AEs/SAEs and drug accountability.

5.3.2 Procedures for handling patients incorrectly initiated on investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

Where patients who do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the investigator should inform the Sponsor Study Physician immediately. The decision on when to discontinue the ineligible patient from the study is based on the medical/safety risk for the patient. The Sponsor Study Physician is to ensure all such contacts are appropriately documented.

5.3.3 Procedures for withdrawal from study

Patients are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen by an investigator and undergo the assessments and procedures scheduled for the post study assessment (see Section 6.4.6). Adverse events should be followed up (see Sections 6.5.3 and 6.5.4) and the patient should return study drug.

5.3.4 Continued access to study intervention after the end of the study

Dizal Pharma will provide continued access to the investigational drug after the end of the study to patients who still benefit from the treatment according to the investigator.

The following criteria must be met in order to apply for continued access:

- There are no appropriate alternative treatments available to the patient
- Treatment duration not exceeding two years (approximately 35 cycles)
- Dizal Pharma has sufficient supply of the investigational drug to provide continued treatment.

- Continued access does not oblige Dizal Pharma to manufacture a new batch of the interventional drug.
- Available data suggests that the investigational drug is safe.
- Out of study continued access is allowed in the respective country.

6. STUDY PLAN AND COLLECTION OF STUDY VARIABLES

6.1 Study Plan

Descriptions of the procedures are included in Table 2 and Table 3 (Part A and Part B, respectively). The schedule of assessments may change in response to emerging data, updated assessment tables will be provided outside of the protocol. All study visits from Cycle 3 Day 1 onwards may be performed within a visit window of ± 2 days.

Table 2 Visit schedule (Part A: dose escalation and extension cohorts)

Study Cycles (21 days for one cycle)	Screen[A]	C1			C2	C3	C4	C5	C6	C7	C8	C9	C10 onwards	End of treatment	28-day Follow-up[B]	Section
Day	-28 to -1	1	8	15	1	1	1	1	1	1	1	1	1			
Informed consent	×															4
Medical history and demographics	×	×														6.3
Inclusion/exclusion criteria	×															4
Physical examination	×	×			×	×	×	×	×	×	×	×	×	×		6.4.1
ECOG PS	×	×			×	×	×	×	×	×	×	×	×	×		6.4.1
Vital Signs (BP/HR)	×	×*	×	×	×*	×	×	×	×	×	×	×	×	×		6.4.2
Body temperature	×	×			×	×	×	×	×	×	×	×	×	×		6.4.2
Height	×															6.4.2
Weight	×	×			×	×	×	×	×	×	×	×	×	×		6.4.2
HBV, HCV. HIV screening	×															6.4.5
TB screening (PPD test or X-ray/CT)	×															6.3.1
Brain MRI	×															6.3.1
Pulmonary Function Tests[C]	×					×		×		×		×, then every 2 cycles				6.4.5
Concomitant medications	×	×	=	=	=	=	=	=	=	=	=	=	=	×	×	4.3
AE evaluation[D]	×	×	=	=	=	=	=	=	=	=	=	=	=	×	×	6.5
12-lead ECG	×	×*	×	×	×*	×	×	×	×	×	×	×	×	×		6.4.3
Echocardiogram/MUGA[E]	×					×				×, then every 4 cycles						6.4.5
Hematology[F]	×	×	×	×	×	×	×	×	×	×	×	×	×	×		6.4.4
Serum chemistry[F]	×	×	×	×	×	×	×	×	×	×	×	×	×	×		6.4.4

Study Cycles (21 days for one cycle)	Screen[A]	C1			C2	C3	C4	C5	C6	C7	C8	C9	C10 onwards	End of treatment	28-day Follow-up[B]	Section
Day	-28 to -1	1	8	15	1	1	1	1	1	1	1	1	1			
Coagulation[F]	×	×	×	×	×	×	×	×	×	×	×	×	×	×		6.4.4
Urinalysis[F]	×	×	×	×	×	×	×	×	×	×	×	×	×	×		6.4.4
Pregnancy test (pre-menopausal females only)	×	×												×		6.4.4
Archived or freshly obtained tumor sample for genetic aberration and protein expression detection[G]	×															6.7.2
Plasma PK		×*	×	×	×*	×	×									6.6.1
Whole blood for ex vivo pSTATs[H]		×*		×												6.7.1
Blood for mutation detection[I]	×															6.7.1
CT Scan (with contrast unless contraindicated)[J]	×					×			×			× . then every 3 cycles				6.9.1
PET[K]	×					×			×							6.9.2
Bone marrow aspiration and biopsy[L]	×															6.9.1
AZD4205 administration[M]		×	=	=	=	=	=	=	=	=	=	=	×			5

Footnote for Schedule of Study Activities (Part A):

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

A. Screening tests should be performed within 28 days before the first administration of study drug.
B. A safety follow up visit will occur 28 days (±7) from the last dose of study drug.
C. PFTs (including spirometry and DLCO) will be performed at screening, Cycle 3 Day 1 and then every 6 weeks and whenever clinically indicated.
D. AEs will be collected and recorded in CRF from first dosing of AZD4205 until the end of the follow up period (28 ±7 days post lase dose). However, SAE should be recorded in CRF from ICF signing to the end of defined follow-up period.

E. Echocardiogram or MUGA scan to assess LVEF will be conducted at screening (prior to first dose of AZD4205), Cycle 3 Day 1, then every 12 weeks for the rest of cycle.
F. Laboratory tests do not need to be repeated at baseline if the baseline visit is within 7 days of the screening sample.
G. All patients will be requested to provide archived or freshly-obtained tumor samples to explore potential genetic factors and protein expression that may have impact on clinical outcome in patients treated with AZD4205.
H. Blood sampling for pSTATs inhibition of blood cells is only mandatory for patients enrolled in the designated sites in the extension cohorts.
I. All patients will be requested to provide blood samples at screening to evaluate genetic mutations in ctDNA including, but not limited to JAK/STAT mutation status of patients.
J. Pre-treatment tumor assessment should be performed within 28 days prior to (preferably close to) the first dose, including a computed tomography (CT) scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites (e.g., neck). During treatment, CT scans will be done for tumor assessments within 7 days of Day 1 of Cycle 3, 6, 9 and then every 3 cycles thereafter until PD.
K. PET scan is required for the pre-treatment tumor assessment. During treatment, PET is mandatory for patients with FDG-avid disease on Day 1 of Cycle 3 and 6 (within 7 days), and when need to confirm a complete remission.
L. A bone marrow aspirate and biopsy will be done at screening. During treatment, bone marrow aspirate and biopsy will only be required to confirm any complete remission for patients with bone marrow involvement at screening and when clinically indicated.
M. Treatment may continue until disease progression, unacceptable toxicity, discontinuation criteria have met, withdrawal of consent or termination of the study by Sponsor. All patients need to take prophylaxis for pneumocystis carinii pneumonia (PCP) infection per European Conference on Infections in Leukemia (ECIL) (Maertens J et al. 2016, Cordonnier C et al. 2016).

Table 3 Visit schedule (Part B: dose expansion cohort)

Study Cycles (21 days for one cycle)	Screen[A]	C1			C2	C3	C4	C5	C6	C7	C8	C9	C10 onwards	End of treatment	28-day Follow-up[B]	Post progression survival F/U[C]	Section
Day	-28 to -1	1	8	15	1	1	1	1	1	1	1	1	1			3 monthly relative to progression	
Informed consent	×																4
Medical history and demographics	×	×															6.3
Inclusion/exclusion criteria	×																4
Physical examination	×	×			×	×	×	×	×	×	×	×	×	×			6.4.1
ECOG PS	×	×			×	×	×	×	×	×	×	×	×	×			6.4.1
Vital Signs (BP/HR)	×	×*	×	×	×*	×	×	×	×	×	×	×	×	×			6.4.2
Body temperature	×	×			×	×	×	×	×	×	×	×	×	×			6.4.2
Height	×																6.4.2
Weight	×	×			×	×	×	×	×	×	×	×	×	×			6.4.2
HBV, HCV, HIV screening[D]	×																6.4.5
TB screening (PPD test or X-ray/CT)	×																6.3.1
Brain MRI	×																6.3.1
Pulmonary Function Tests[E]	×					×		×		×		×. then every 2 cycles					6.4.5
Concomitant medications	×	×	=	=	=	=	=	=	=	=	=	=	=	×	×		4.3
AE evaluation[F]	×	×	=	=	=	=	=	=	=	=	=	=	=	×	×		6.5
12-lead ECG	×	×*	×	×	×*	×	×	×	×	×	×	×	×	×			6.4.3
Echocardiogram/MUGA[G]	×					×				×. then every 4 cycles							6.4.5

Study Cycles (21 days for one cycle)	**Screen[A]**	**C1**			**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10 onwards**	**End of treatment**	**28-day Follow-up[B]**	**Post progression survival F/U[C]**	**Section**
Day	-28 to -1	1	8	15	1	1	1	1	1	1	1	1	1			3 monthly relative to progression	
Hematology[H]	×	×	×	×	×	×	×	×	×	×	×	×	×	×			6.4.4
Serum chemistry[H]	×	×	×	×	×	×	×	×	×	×	×	×	×	×			6.4.4
Coagulation[H]	×	×	×	×	×	×	×	×	×	×	×	×	×	×			6.4.4
Urinalysis[H]	×	×	×	×	×	×	×	×	×	×	×	×	×	×			6.4.4
Eye examinations	×					×			×			×, then every 3 cycles		×			6.4.5
Pregnancy test (pre-menopausal females only)	×	×												×			6.4.4
Tumor sample for pathology confirmation[I]	×																4
Plasma PK[J]		×*		×	×*		×		×								6.6.1.2
Whole blood for ex vivo pSTATs[K]		×*		×													6.7.1
Blood sample for pharmacogenetics research (optional)[L]	×																6.7.1
CT Scan (with contrast unless contraindicated)[M]	×					×			×			×, then every 3 cycles					6.9.1
PET[N]	×					×											6.9.2
Bone marrow aspiration and biopsy[O]	×																6.9.1
AZD4205 administration[P]		×	=	=	=	=	=	=	=	=	=	=	×				5
Survival[C]																×	6.9.5

Footnote for Schedule of Study Activities (Part B):

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

A. Screening tests should be performed within 28 days before the first administration of study drug.
B. A safety follow up visit will occur 28 days (±7) from the last dose of study drug.
C. In the Phase 2 expansion, following disease progression, the patient, patient's family, or the patient's current physician must be contacted every 3 months for survival information, for collection of details of subsequent treatment regimens received following withdrawal from study drug and to follow up unresolved AEs (unless the patient withdraws consent) regardless of date of last contact.
D. Both HBsAg and HBcAb should be negative for eligibility.
E. PFTs (including spirometry and DLCO) will be performed at screening, Cycle 3 Day 1 and then every 6 weeks and whenever clinically indicated.
F. AEs will be collected and recorded in CRF from first dosing of AZD4205 until the end of the follow up period (28 ±7 days post lase dose). However, SAE should be recorded in CRF from ICF signing to the end of defined follow-up period.
G. Echocardiogram or MUGA scan to assess LVEF will be conducted at screening (prior to first dose of AZD4205), Cycle 3 Day 1, then every 12 weeks for the rest of cycle.
H. In the Phase 2 expansion, laboratory tests for screening should be performed within 7 days prior to the planned first dosing date. In addition, laboratory tests do not need to be repeated at baseline if the baseline visit is within 3 days of the screening sample.
I. In the Phase 2 expansion, submission of the tumor block or unstained slides from a diagnostic biopsy is required for retrospective central confirmation of disease histologic subtype. The diagnostic specimen needs to be from a malignant lymph node or extra-nodal tissue obtained by excisional biopsy.
J. Patients at the selected sites will be invited for intense PK study on Cycle 1 Day 1 and Cycle 2 Day 1.
K. Blood sampling for pSTATs inhibition of blood cells is only mandatory for patients enrolled in the designated sites.
L. Blood sampling for pharmacogenetics research at screening is optional for patients enrolled in the Part B.
M. Pre-treatment tumor assessment should be performed within 28 days prior to (preferably close to) the first dose, including a computed tomography (CT) scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites (e.g., neck). During treatment, CT scans will be done for tumor assessments within 7 days of Day 1 of Cycle 3, 6, 9 and then every 3 cycles thereafter until PD.
N. PET scan, where available, needs to be performed for the pre-treatment tumor assessment. During the treatment, PET should be performed on Day 1 of Cycle 3 (within 7 days) and when need to confirm a complete metabolic remission, if FDG-avid disease is detected based on baseline PET scan. Patients with confirmed CR are not required to undergo further PET scans on study unless there is suspicion of progressive disease.
O. A bone marrow aspirate and biopsy will be done at screening (or within 60 days prior to the first dose of AZD4205). During treatment, bone marrow aspirate and biopsy will only be required to confirm any complete remission for patients with bone marrow involvement at baseline (screening) and when clinically indicated.
P. Treatment may continue until disease progression, maximum duration of treatment, unacceptable toxicity, discontinuation criteria have met, withdrawal of consent or termination of the study by Sponsor. All patients need to take prophylaxis for pneumocystis carinii pneumonia (PCP) infection per European Conference on Infections in Leukemia (ECIL) (Maertens J et al. 2016, Cordonnier C et al. 2016).

6.2 Recording of data

Web Based Data Capture (WBDC) will be used for data collection and query handling. The investigator will ensure that data are recorded on the CRFs as specified in the protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and for the provision of answers to data queries according to the Clinical Study Agreement or applicable information. The investigator will sign the completed CRFs. A copy of the completed CRFs will be archived at the study site.

6.3 Screening procedures and baseline assessment

6.3.1 Enrollment and screening

At enrollment, each potential patient will provide informed consent prior to starting any study specific procedures. The screening procedures are summarized in Table 2 and Table 3.

Each potential patient is assigned a unique enrollment number. If a patient withdraws from the study, then the enrollment code cannot be reused.

A standard medical, medication and surgical history will be obtained with review of the selection criteria with the patient.

Each patient will undergo screening (Table 2 and Table 3) up to 28 days prior to first dosing to confirm eligibility. TB screening will be done using PPD test or chest X-ray/CT or following local practice. Tumor assessments and other clinical data obtained as standard of care prior to consent may be used for the study provided the assessments fall within the protocol specified period prior to the first dose of study drug.

All patients should have Brain MRI within 28 days of first dose to exclude CNS lymphoma.

Prior to discharge from each in-patient and clinic visit, the Investigator or their deputy will be responsible for reviewing all available data including vital signs and ECG tracings.

6.3.2 Patient demographics/Other baseline characteristics

Demographic data and other characteristics will be recorded and will include date of birth or age, gender, race and/or ethnicity according to local regulations.

The important findings of medical, medication and surgical history during eligibility review (i.e. previous diagnoses, disease, surgeries and current medication) will be collected and captured in the eCRF.

Disease background information will be collected, including:

1. Pathology (pathological subtype).
2. History of lymphoma and current disease status/staging (see Table 4).
3. Bone marrow involvement status.

4. History of prior anti-cancer treatment, i.e. chemotherapy(ies), HDAC inhibitor(s), CD30 targeting therapy(ies) for CD30+ subtypes, and ALK inhibitor(s) for ALCL-ALK+.
5. History of radiotherapy.
6. History of stem cell transplantation. The patients enrolled in this study should be transplant-ineligible, and their reasons for ineligibility should be collected, i.e. disease status (active disease), comorbidities or other factors.

Table 4 Revised Ann Arbor Staging System

Stage	Involvement	Extra-nodal (E) status
Limited		
I	One node or a group of adjacent nodes	Single extra-nodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extra-nodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

Note: Extent of disease is determined by PET/CT for avid lymphomas and computed tomography for non-avid histology. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.
Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

6.4 Safety procedures

6.4.1 Physical examination

A complete physical examination will be performed at the visits as indicated in the Study Plan (see Table 2 and Table 3). The assessment should include, but not limit to, the following body systems: general appearance, skin, lymph nodes, musculoskeletal/extremities, cardiovascular, lungs, abdomen, and neurological.

Performance status will be assessed at the visits as indicated in the Study Plan (see Table 2 and Table 3). The ECOG performance status below includes scales and criteria used to assess how a patient's disease is progressing and how the disease affects the daily living abilities of the patient, and to determine appropriate treatment and prognosis. Performance status will be assessed at screening, prior to first dose of each cycle, and at discontinuation 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 e.g., 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.

6.4.2 Vital signs

Supine blood pressure and pulse rate

Supine blood pressure and pulse rate will be measured after 10 minutes rest. Assessments will be performed at the visits as shown in the Study Plan (see Table 2 and Table 3). Observations will be recorded at the following times:

- **Part A Dose escalation and extension cohorts**
  - Screening.
  - First day of multiple dosing (Day 1 Cycle 1): pre-dose and 1, 2, 4, 8, 24 hours post first dose.
  - Presumed steady state (Day 8 and Day 15 of Cycle 1): pre-dose.
  - Presumed steady state (Day 1 Cycle 2): pre-dose, 1, 2, 4, 8 hours post dose.
  - On Day 1 of each subsequent Cycle: one assessment at any time during day.
  - On occurrence of any cardiac AE.
  - Discontinuation visit.
- **Part B Dose expansion cohort**
  - Screening.
  - First day of multiple dosing (Day 1 Cycle 1): pre-dose and 1, 2, 4, 8 hours post first dose.
  - Presumed steady state (Day 8 and Day 15 of Cycle 1): pre-dose.
  - Presumed steady state (Day 1 Cycle 2): pre-dose, 1, 2, 4, 8 hours post dose.
  - On Day 1 of each subsequent Cycle: one assessment at any time during day.
  - On occurrence of any cardiac AE.
  - Discontinuation visit.

Time points of measurement may be adjusted on the basis of emerging PK and safety data. Patients with dose interruption do not require multiple monitoring of vital signs during the period of the dose interruption.

Body temperature

Body temperature will be measured in degrees Celsius at the screening and then Day 1 of each cycle, and at the discontinuation visit, as indicated in the Study Plan (Table 2 and Table 3).

Weight

Weight will be performed at screening and then Day 1 of each cycle and at the discontinuation visit.

Height

Height will be assessed at screening only.

Vital signs should be assessed additionally at the discretion of the Investigator if clinically indicated. There is a +/- 15-minute window for the collection of vital signs performed at pre-dose and 1-10 h, and a 1-hour window for vital sign assessment performed at 24 h. The timing and frequency of vital sign assessment may be adjusted in response to the emerging PK and safety profile. Any changes in vital signs should be recorded as an AE if applicable.

6.4.3 ECG

Resting 12-lead ECG

Twelve - lead triplicate ECG will be performed at the visits as shown in Study Plan (Table 2 and Table 3) at the following time points:

- **Part A Dose escalation and extension cohorts**
  - Screening.
  - First day of multiple dosing (Day 1 Cycle 1): pre-dose, 1, 2, 4, 8 and 24 hours post dose.
  - Presumed steady state (Day 8 and Day 15 of Cycle 1): pre-dose.
  - Presumed steady state (Day 1 Cycle 2): pre-dose, 1, 2, 4, 8 hours post dose.
  - Day 1 Cycle 3 and Day 1 Cycle 4: pre-dose.
  - On Day 1 of each subsequent Cycle: one assessment at any time during day.
  - On occurrence of any cardiac AE.
  - Discontinuation visit.
- **Part B Dose expansion cohort**
  - Screening.
  - First day of multiple dosing (Day 1 Cycle 1): pre-dose, 1, 2, 4 and 8 hours post dose.
  - Presumed steady state (Day 8 and Day 15 of Cycle 1): pre-dose.
  - Presumed steady state (Day 1 Cycle 2): pre-dose, 1, 2, 4, 8 hours post dose.

- On Day 1 of each subsequent Cycle: one assessment at any time during day (except pre-dose on Day 1 of Cycle 4 and 6).
- On occurrence of any cardiac AE.
- Discontinuation visit.

The timing and number of ECGs may be adjusted in response to the emerging PK and safety data. Patients with dose interruption do not require multiple monitoring of ECG during the period of the dose interruption.

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine/supine for at least 10 minutes prior to each time point indicated. All ECGs should be recorded with the patient in the same physical position. For each time point, all three ECGs should be taken at about 5-minute intervals, and the triplicate ECGs should be done within 15 minutes before corresponding PK sampling, including pre-dose and 1 - 8 h post-dose. As for 24 h post-dose ECGs, all three recordings should be performed within 1 hour before corresponding PK sampling.

A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study, where feasible.

After paper ECGs have been recorded, the investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records. 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 medical history condition. If there is a clinically significant abnormal ECG findings during the treatment period, this should be recorded on the AE CRF, according to standard adverse events collection and reporting processes (see section 6.5.3 and 6.5.4). It is recommended that asymptomatic ECG findings should be adjudicated by an expert reader in case they are reported as AEs with the ECG abnormaity given as explantory information. For all ECGs details of rhythm, PR, R-R, QRS and QT intervals and an overall evaluation will be recorded. All ECGs of patients with any value > 470 ms QTcF are to be sent for immediated review by the study team.

All ECG data will also be collected digitally for each patient and will be transferred electronically for central analysis as described in the study specific ECG manual (if applicable). Heart rate, PR, R-R, QRS and QT intervals will be determined and reviewed by an external cardiologist (if applicable).

Confirmed QTc prolongation (> 500 msec absolute or > 60 msec above baseline) is the dose interruption criteria.

6.4.4 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, coagulation and urinalysis will be taken at the visits as indicated in the Study Plan (Table 2 and Table 3). Blood samples for laboratory safery assessments should be collected afrer a 8-hour fast (no food or drink, except water).

Blood and urine samples for safety assessment will be collected at the following times:

- Screening.
- Weekly during Cycle 1: Pre-dose on Day 1, Day 8 and Day 15.
- On Day 1 of each subsequent Cycle: Pre-dose.
- Discontinuation visit.

The date and time of each collection will be recorded in the appropriate CRF.

The timing of blood samples may be altered depending on the emerging PK and safety profile. Additional sampling times may be added if indicated by the emerging data.

Laboratory values that meet the criteria for CTCAE Grade 3 or have changed significantly from baseline and are considered to be of clinical concern will be repeated/confirmed within 7 days and followed up as appropriate.

The following laboratory variables will be measured during study:

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

aPTT = activated partial thromboplastin time; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; PTT = partial thromboplastin time.

*High sensitivity cTnT (hs-cTnT) assay (if applicable) is recommended.

** In case of positive urine blood test, assessment of red blood cell count in urine should be performed.

*** In case of positive urine leucocytes test, assessment of leucocytes count in urine should be performed.

In addition, sample will be collected from all females of child-bearing potential at screening, before the first dose, and at treatment discontinuation for a pregnancy test. In case a patient shows an AST

or ALT ≥ 3 × ULN or total bilirubin ≥ 2 × ULN please refer to Appendix III. HY's Law 'Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law' for further instructions.

6.4.5 Other safety assessments

Echocardiogram/MUGA Scan

Echocardiogram or MUGA scan to assess LVEF will be conducted at screening (prior to first dose of AZD4205), Cycle 3 Day 1, then every 12 weeks for the rest of cycle. Additional Echocardiogram or MUGA scan will be performed whenever necessary as clinically indicated throughout the study.

The modality of the cardiac function assessments must be consistent within a patient i.e. if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans if required. The patients should also be examined using the same machine and operator whenever possible, and a quantitative measurements should be taken. Recommendations include having complete high quanlity standardized 2-D with Doppler echocardiographic examinations performed by an experienced sonographer and include evaluation of both systolic and diastolic left ventricular function. Ejection fraction determinations should be determined quantitatively based on bi-plane measurements of end diastolic and end systolic left ventricular volumes.

An asymptomatic LVEF decrease to < 40% or LVEF [40-54%] and LVEF decrease ≥ 10% from baseline or any symptomatic LVEF decrease are the dose interruption criteria. Any symptomatic decrease in LVEF will prompt the discontinuation of the treatment and a cardiac consultation.

Pulmonary function tests (PFTs)

Signs and symptoms (cough, short breath and pyrexia, etc) including auscultation for lung field will be checked at each visit.

PFTs (including spirometry and DLCO) will be performed at screening, Cycle 3 Day 1 and then every 6 weeks and whenever clinically indicated.

HRCT scan will be performed when clinically indicated (see below, details could be found in Appendix VII. Guidance for the Safety Monitering and Management of Adverse Events):

- If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of interstitial lung disease on CT scan or decrease in lung function tests (DLCO decrease ≥ 15%) is observed, the study treatment dosing should be interrupted and a full diagnostic workup (including chest X-Ray with PA and lateral view, cardiac, infectious and hematological workups) will be performed. **A full diagnostic workup is strongly recommended** to exclude alternative causes such as infection, disease progression and cardiac causes. Alternative clinical diagnosis will be managed according to local practice.
- If other causes of respiratory changes have been excluded an HRCT scan should be performed. If a diagnosis of drug-induced pneumonitis is confirmed, study treatment

should be permanently discontinued. In the absence of a diagnosis of drug-induced pneumonitis, study treatment may be restarted.

Hepatitis screen, HIV screen

All patients will be screened for Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (HBcAb). Both HBsAg and HBcAb should be negative for eligibility.

Screening for Hepatitis C will be based on HCV antibodies.

Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site, e.g. Western blot.

Appropriate counselling will be made available by the Investigator in the event of a positive finding. Notification of regional and/or national authorities, if required by law, will be the responsibility of the Investigator.

Ophthalmic examinations

Ophthalmic examinations by specialist should be performed for all patients at baseline, Cycle 3 and then every 3 cycles (approximately every 2 months) after enrolment. The recommended ophthalmic examinations include visual acuity (corrected), intraocular pressure, slit lamp examination, and dilated ophthalmoscopy. For the grading and clinical management of ocular adverse events, refer to Appendix VII.

6.4.6 Safety follow-up

An end of study treatment assessment will be performed at the time investigational product is permanently discontinued (see Table 2 and Table 3).

In addition, a 28-day follow-up should be made by telephone contact after 28 days (± 7 days) following the discontinuation of the study treatment to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy). Refer to section 6.5.3 for full details on AE recordings during follow-up.

6.5 Adverse events

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

6.5.1 Definition of adverse events

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any deterioration of the disease under study and associated symptoms or findings should not be regarded as an adverse event as far as the deterioration can be anticipated.

The term adverse event is used generally to include any AE whether serious or non-serious.

6.5.2 Definitions of serious adverse events

A serious adverse event (SAE) is an AE occurring during any study phase (i.e., screen, treatment, washout, and follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity or substantial disruption of the ability to conduct normal life functions
- Is or results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix IV of this Clinical Study Protocol.

6.5.3 Recording of adverse events

Time period for collection of adverse events

AEs will be collected and recorded in eCRF from first dosing of AZD4205 until the end of the follow up period. The follow-up period is defined as 28 days (± 7 days) after study treatment is discontinued. However, SAE should be collected and recorded in eCRF from ICF signing to the end of defined follow-up period (see Table 5).

Table 5 Summary of recording and follow-up of adverse events

	Consent to Randomization/first dosing	Until defined Follow up Visit (safety follow-up period)	Post Follow-up visit but prior to progression (if applicable)
Record all new AEs in CRF	No*	Yes	No
Record all ongoing AEs in CRF	No	Yes	No**
Record all study procedure related new SAEs in CRF	Yes	Yes	No***

* Adverse events prior to the first dosing but worsening post the first doing should be recorded in eCRF as new AEs.
** All ongoing AEs/SAEs post safety follow-up period will be followed by investigator as long as medically indicated, but without further collection in eCRF.
*** New emerging SAEs post follow-up period including death should not be collected in eCRF, but still need to be reported to Dizal in the condition of causality with study procedure judged by investigator.

After the final database lock, there may be some patients remaining on study treatment. For these patients who are continuing to receive AZD4205, Sponsor will collect information (during the treatment period and for 28 +/- 7 days after last dose) on SAEs, deaths (including those due to disease progression), discontinuation due to AEs/SAEs and drug accountability only.

Follow-up of unresolved adverse events

Sponsor retains the right to request additional information for any patient with ongoing AE(s) at the end of the study, if judged necessary.

If an investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to AZD4205, the investigator should notify Sponsor.

Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date when the AE started, stopped and intensity changed
- CTCAE grade (version 5.0); for the grading of specific ocular AEs, refer to Appendix VII (Table 18)
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- Outcome
- For SAEs other variables will be collected including treatment given for the event.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.5.2. 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. 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.

The grading scales found in the current National Cancer Institute CTCAE version will be utilized 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 current CTCAE version can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

Causality collection

The investigator will assess causal relationship between investigational product 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 investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedure. 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 IV of this Clinical Study Protocol.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: *'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 CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) other than recording of 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.

Adverse events based on examinations and tests

The criteria for determining whether an abnormal examination finding, or laboratory parameter should be reported as an adverse event are as follows:

- Abnormal examination finding or laboratory result is accompanied with symptoms, and/or
- Abnormal examination finding or laboratory result requires or medical/surgical intervention, and/or
- Abnormal examination finding or laboratory result leads to a change in study dosing or discontinuation from the study, additional concomitant drug treatment, or other therapy, and/or
- Abnormal examination finding or laboratory result is considered to be an adverse event by the investigator or sponsor.

Abnormal examination finding or laboratory result which meets criteria above should be considered as clinically significant. Purely repeating an abnormal test, in the absence of any of the above conditions, is not considered an adverse event.

If an abnormal examination finding or laboratory parameter is associated with clinical signs and symptoms, the sign or symptom (preferably the diagnosis) will be reported as an AE and the associated laboratory result or other finding will be considered as additional information. If an abnormal examination finding or laboratory parameter is a sign of a disease or syndrome, only the diagnosis should be recorded as AE in CRF (e.g. both AST and ALT increase and reach AE criteria based on CTCAE, the AE term in CRF should be recorded as one AE of increased liver enzyme). Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value).

Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease (symptomatic progression). The development of new, or progression of existing metastasis to the primary cancer under study should be considered as radiological disease progression and not an AE. Events that

are unequivocally due to symptomatic or radiological disease progression should not be reported as AEs during the study.

New cancers

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

Hy's Law

Cases where a patient shows an AST or ALT $\geq 3\times$ULN and total bilirubin $\geq 2\times$ULN may need to be reported as SAEs. Prompt reporting of cases meeting Hy's law criteria (via the SAE expedited reporting system) is required for compliance with regulatory guidelines. The investigator is responsible for, without delay, determining whether a patient meets potential Hy's law criteria. Details of identification of potential Hy's law cases and actions to take are detailed in Appendix III. HY's Law.

Handling of deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of investigational product, should be reported as follows:

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the CRF module, but should not be reported as a SAE during the study.
- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.
- Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to Sponsor representative within the usual timeframes.

6.5.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). SAEs should be reported to Dizal and recorded in CRF according to Section 6.5.3.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate Sponsor representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all the necessary information is provided to appropriate patient safety database within one calendar day of initial receipt for fatal and life-threatening events and within five calendar days of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Sponsor representatives of any follow-up information on a previously reported SAE immediately, or no later than 24 hours of when he or she becomes aware of it. The SAE will be reported to the designated sponsor representative via the study SAE paper form.

The Sponsor representative will advise the investigator/study site personnel how to proceed.

6.6 Pharmacokinetics

6.6.1 Collection of PK samples

6.6.1.1 Part A Dose escalation and extension cohorts

Samples to evaluate the PK of AZD4205 will be taken. Estimated sampling time points are shown here. Discussions will be required with the Dizal PK representative as to any effect on the PK sample schedule if dose interruption occurs within 3 days of PK sampling. The date and time of collection of each sample and the date and time of dose will be recorded. The timing of the PK samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterization of the plasma concentration-time profiles. Updated timings will be provided outside of the protocol and will be documented.

A 5 min window will be allowed for samples taken at 0.5 h and 1 h; a 10 min window for samples taken at 1.5 - 10 h; a 15 min window for samples taken at pre-dose; a 1 h window for samples taken at 24 h.

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

Cycle 1 (multiple once daily dosing):

Day 1 (PK profile on day 1 within 24 hr): Pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 24 hours post-dose (**prior to next dose**).

Day 8 and 15: Trough blood sample (pre-dose, 2 mL). Plasma samples (~ 1 mL) will be used for quantification of AZD4205.

Collect PK blood samples (approximately 2 mL each time point) using 2 mL lavender top (EDTA) Vacutainer® evacuated collection tubes at the time points indicated. The date and time of collection of each sample will be recorded. Plasma samples (~1 mL) will be used for quantification of AZD4205.

Cycle 2 (multiple once daily dosing):

Day 1 (PK profile at steady state): Pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 24 hours post-dose (**prior to next dose**).

Collect PK blood samples (approximately 2 mL each time point) using 2 mL lavender top (EDTA) Vacutainer® evacuated collection tubes at the time points indicated. The date and time of collection of each sample will be recorded. Plasma samples (~1 mL) will be used for quantification of AZD4205.

Cycle 3 and 4 (multiple once daily dosing):

Day 1: Trough sample (pre-dose, 2 mL) Plasma samples (~1 mL) will be used for quantification of AZD4205.

Collect PK blood samples (approximately 2 mL each time point) using 2 mL lavender top (EDTA) Vacutainer® evacuated collection tubes at the time points indicated in Table 6. The date and time of collection of each sample will be recorded. Plasma samples (~1 mL) will be used for quantification of AZD4205.

Table 6 PK blood sampling schedule (Part A)

Time relative to dose	Cycle 1 (multiple dose)			Cycle 2 (multiple dose)	Cycle 3 (multiple dose)	Cycle 4 (multiple dose)
	Day 1	Day 8	Day 15	Day 1	Day 1	Day 1
Pre-dose	×	×	×	×	×	×
0.5 hours	×			×		
1 hour	×			×		
1.5 hours	×			×		
2 hours	×			×		
2.5 hours	×			×		
3 hours	×			×		
4 hours	×			×		
6 hours	×			×		
8 hours	×			×		
10 hours	×			×		
24 hours	×			×		

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

6.6.1.2 Part B Dose expansion cohort

About 20% of the total patients at the selected sites will be invited for intense PK study on Cycle 1 Day 1 and Cycle 2 Day 1. The remaining patients will be invited for sparse PK study on Cycle 1 Day 1 and Cycle 2 Day 1.

Venous blood samples (2mL) per visit in time windows (defined in the following table) will be taken at the times presented in Table 7 and Table 8 for determination of AZD4205 in plasma. A 5

min window will be allowed for samples taken at 1 h; a 10 min window for samples taken at 2-8 h; a 15 min window for samples taken at pre-dose; a 1 h window for samples taken at 24 h.

The date and time of collection of each sample and the date and time of dose (on PK sampling day and for previous dose) will be recorded.

Table 7 PK blood samples schedule for intense PK study (Part B)

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

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

Table 8 PK blood sampling schedule for sparse PK study (Part B)

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

6.6.2 Determination of drug concentration in PK samples

PK samples will be analyzed by CRO chosen by Sponsor using an appropriate bioanalytical method. The concentration of AZD4205 in plasma will be measured to understand its PK. Full details of the analytical method used will be described in a separate bioanalytical report. All samples still within the known stability of the analytes of interest (i.e., AZD4205) at the time of receipt by the bioanalytical laboratory will be analyzed.

PK samples remaining in this study may be used for metabolite quantification or biomarker analyses (i.e. plasma 4β-hydroxy cholesterol and total cholesterol quantification for the evaluation on the changes of CYP3A activity upon AZD4205 treatment). Data from this residual samples will be reported separately from the Clinical Study Report.

In addition, the pharmacokinetic samples may be subjected to further analyses by Dizal or other CROs in order to further investigate the presence and/or identity of additional drug metabolites. Any results from such analyses will be reported separately from the Clinical Study Report.

Details on sample processing, handling, shipment and storage are provided in the Laboratory Manual.

[redacted]

[redacted]

[redacted]

6.8 Biological sampling procedures

6.8.1 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described below.

Biological samples for future research will be retained at Sponsor or it's designee for a maximum of [redacted] following the finalization of the Clinical Study Report. The results from future analysis will not be reported in the Clinical Study Report but separately in a bioanalytical report.

6.8.1.1 Blood Sample

After collection, blood samples will be aliquoted and put into different tubes for safety, PK and biomarker assessments.

6.7.1.1.1Safety assessments

Safety laboratory assessments will be performed locally at each center's laboratory by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change.

6.7.1.1.2 PK assessments

PK samples will be disposed of six months after the Bioanalytical Report finalization, unless requested for future analyses.

PK samples may be disposed of or destroyed and anonymized. Additional analyses may be conducted on the anonymized, PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR. Anonymized samples will be retained for no more than [redacted] after the CSR is finalized.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report.

Any PK sample remaining may be used for metabolite quantification or biomarker analyses (i.e. 4β-hydroxy cholesterol and total cholesterol). These analyses are for Sponsor use only and will not be included in the Clinical Study Report.

[redacted]

[redacted]

[redacted]

6.8.1.2 Tumor sample

In Part A, archived or freshly obtained tumor samples will be used to explore potential genetic factors and protein expression that may have impact on clinical outcome in patients treated with AZD4205 in PTCL.

When formalin fixed paraffin embedded (FFPE) block is not possible, unstained sections should be prepared from the FFPE sample block. Tissue sectioning will be cut onto positively-charged glass slides at appropriate time upon sponsor's request. All blocks or sections must be put into appropriate containers with clear labelling. Finally, the blocks or slides should be shipped in an appropriate condition.

In Part B, submission of tumor block (or $\geq$ 12 unstained slides) from an excisional biopsy from nodal or extra-nodal lymphoma tissue is required for retrospective central confirmation of pathological diagnosis of PTCL and its subtype.

6.8.2 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix V of this Clinical Study Protocol 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples taken from the patient unless agreed with Sponsor and appropriate labelling, shipment and containment provisions are approved.

6.8.3 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle, including collection, shipment, storage, use, disposal and return. All samples should be identified by a special code. Under no circumstances, should patients' personal information appear on the samples.

The Principal Investigator at each center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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 documentation of receipt of arrival.

Samples kept in sponsor or the third party should be dynamically managed and monitored by sample database system for their shipment, usage and storage. If patient withdraw his/her consent on usage of bio-samples or request to return/dispose of his/her bio-samples, the disposal of patient's samples also should be traced through the database.

Sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the Sponsor biobank system or the designated third party during the entire life cycle.

6.8.4 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of voluntarily donated biological samples, then the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, Sponsor is not obliged to destroy the results of this research.

If collection of the biological samples is an integral part of the study, then the patient may be withdrawn from further participation in the study.

The Principal Investigator:

- Ensures Sponsor is notified immediately of the patient's withdrawal of informed consent to the use of donated biological samples.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the patient and Sponsor are informed about the sample disposal.

Sponsor ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the document returned to the study site.

Sponsor designated research center will conduct potential exploratory biomarker studies if required. Samples will be stored for a maximum of [redacted] following the finalization of the Clinical Study Report. The results from future analysis will not be reported in the CSR but separately in a CSR Addendum /Scientific Report or Scientific Publication.

At the end of the study, or in the event of a participant withdrawing consent, or as required by law, the sponsors will return any samples and delete the Study Data in a sensitive way, according to local laws and protocols.

6.9 Anti-tumor activity

Disease response in this study will be assessed according to the 2014 Lugano classification (Cheson BD et al. 2014), which is widely used in clinical trials as well as in clinical practice for anti-tumor efficacy assessment of lymphoma. The criteria recommend a response assessment in lymphoma according to morphological tumor shrinkage on CT and/or lesion metabolic decrease on PET (see Table 9).

Table 9 Response categories based on Lugano response criteria (Cheson BD et al. 2014)

Response	Site	PET based response (Metabolic response)	CT based response (Radiologic response)
Complete response	Target nodes/nodal messes, extra-nodal lesions	Score 1, 2, or 3* with or without a residual mass on 5 point scale (5-PS)	All of the following: 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	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in the marrow	Normal by morphology; if indeterminate, IHC negative
Partial response	Target nodes/nodal messes, extra-nodal lesions	Score 4 or 5 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	All of the following: ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm ×5 mm as the default value When no longer visible, 0 × 0mm For a node > 5 mm × 5 mm, but smaller than the normal, use actual measurement for calculation
	Non-measured lesion	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
	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

Response	Site	PET based response (Metabolic response)	CT based response (Radiologic response)
No response or stable disease	Target nodes/nodal messes, extra-nodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Non-measured lesion	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	Target nodes/nodal messes, extra-nodal lesions	Score 4 or 5 with increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	Progressive disease requires at least 1 of the following PPD progression: 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 ≤ 2cm 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 (e.g., 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
	Non-measured lesion	None	New or clear progression of preexisting non-measured lesions
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Footnote:

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, [^{18}F]fluorodeoxyglucose; GI = gastrointestinal; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; 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.

*A score of 3 in many patients 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 undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two 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 (e.g., liver, spleen, kidneys, and 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 extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., 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 (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

PET 5-PS: 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.

6.9.1 CT imaging for tumor assessment

All patients will be asked to conduct CT scans (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites based on the signs and symptoms as well as bone marrow aspiration/biopsy at screening (within 4 weeks prior to first dosing of AZD4205, bone marrow aspiration/biopsy within 60 days prior to the first dose of AZD4205 is acceptable) for baseline tumor burden assessment.

During treatment, CT scans of the same sites as screening will be done for tumor response assessment within 7 days of Day 1 of Cycle 3, 6, 9 and then every 3 cycles until PD or withdrawal from the study. Any other sites at which new disease is suspected should also be appropriately imaged. Any patient who discontinues study treatment for reasons other than disease progression should have response assessment performed as scheduled in the protocol until disease progression, or death occurs, unless consent is withdrawn. Images for tumor assessment post new anti-cancer therapy will not be collected.

A bone marrow aspiration or biopsy is required to confirm a complete response for patients with bone marrow involvement at baseline.

6.9.2 PET scan for tumor assessment

PET scan, where available, needs to be performed at screening for the baseline assessment of tumor metabolism. During the treatment, PET should be performed on Day 1 of Cycle 3 (within 7 days) and when need to confirm a complete metabolic remission, if FDG-avid disease is confirmed by PET scan at screening. Patients with confirmed complete metabolic remission are not required to undergo further PET scans on study unless there is suspicion of progressive disease.

If disease is not PET-avid at baseline, PET scan is not required during the study treatment.

NOTE: PET/CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality, adheres to the specified slice thickness/scan parameters, and includes the use of IV contrast. Also, the CT images must be separated from the PET data prior to submitting the data, and cannot be transmitted as fused CT/PET images. An MRI may be used in place of CT only for anatomic lesions which cannot be adequately visualized by CT, or for subjects who cannot undergo CT. Magnetic resonance imaging (MRI) may be used for subjects who are either allergic to CT contrast media or have renal insufficiency that per institutional guidelines restricts the use of CT contrast media. MRI exams of the abdomen and pelvis may be performed in lieu of CTs, but MRI exams of the chest are not recommended. In these cases, a non-contrast CT of the chest is recommended to evaluate the lung parenchyma. If MRI is used, the MRI must be obtained at baseline and at all subsequent response evaluations. If MRI is required for any other reason, this must be discussed with the study medical monitor first. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is kept constant throughout a subject's course on study.

6.9.3 Disease assessment

If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

In the event disease progression is suspected due to physical examination or laboratory test, a CT and/or PET scan must be performed to confirm disease progression. If medically appropriate, it is recommended that uncertain disease progression should be confirmed by an alternative diagnostic imaging modality or biopsy, e.g. diagnostic quality CT/biopsy to confirm metabolic disease progression, or cytologic test to confirm malignant effusion. If the investigator is in doubt as to whether progression has occurred, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan (Table 2 and Table 3).

6.9.4 Efficacy endpoints

6.9.4.1 Part A

In Part A, all response assessment images will be reviewed at site. Duplicates may be collected and stored by a Sponsor appointed representative, and sent for independent central review, if deemed appropriate.

The efficacy endpoint in this part includes objective response rate (ORR), duration of response (DOR) and progression free survival (PFS) by local investigators based on the integrated assessment of CT imaging and PET scan.

6.9.4.2 Part B

In Part B, in addition to investigators' assessment, an independent central review of CT images will be conducted for all patients. The results of independent central review are planned to be used to support an NDA submission of AZD4205. Comparison of independent central review and investigators' assessment will also be conducted.

The efficacy endpoint in this part is summarized in Table 11.

Table 10 Efficacy endpoints assessed in Part B

Primary efficacy endpoint	• CT-based ORR assessed by IRC
Secondary efficacy endpoint	• Other CT-based efficacy parameters assessed by IRC, including DoR, CR rate, PFS and TTR • CT-based efficacy endpoints assessed by local investigators
[redacted]	• [redacted]

	• [redacted]

6.9.5 Survival follow-up

End of study treatment assessment needs to be performed at the time when the investigational product is permanently discontinued, and a 28-day follow-up should be made by telephone contact after 28 days (± 7 days) following the discontinuation of the study treatment to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy). Refer to section 6.5.3 for full details on AE recordings during follow-up.

6.9.5.1 Progression free survival follow-up

Patients' tumor response should be followed according to the study plan (Table 2 and Table 3) till confirmed disease progression per Lugano criteria, death or withdrawal of consent. Under circumstances of dose discontinuation for reasons other than progression, response assessments should be continued per study plan until confirmed disease progression.

Beyond the 28-day follow up visit only subsequent cancer therapy and response assessment (if applicable) should be collected.

[redacted]

7. EVALUATION AND CALCULATION OF VARIABLES AND STATISTICAL METHODS

7.1 Definition of study endpoints

7.1.1 Part A Dose escalation and extension cohorts

The primary endpoints are the incidence of adverse events (AEs), serious adverse events (SAEs) and abnormal laboratory test results.

The secondary and exploratory endpoints are as follows:

- Secondary endpoints:
  - PK assessments include AZD4205 concentrations in plasma of individual patient.
  - Preliminary assessments of anti-tumor activity by local investigators per Lugano criteria, including ORR, PFS and DoR.
- [redacted]:

- [redacted]

[redacted]

[redacted]

7.1.2 Part B Dose expansion cohort

The primary endpoints are CT-based ORR assessed by IRC according to Lugano criteria.

The secondary and exploratory endpoints are as follows:

- Secondary endpoints:
  - DOR, CRR, PFS, TTR assessed by IRC based on CT imaging, according to 2014 Lugano classification.
  - Investigators-assessed efficacy endpoints based on CT imaging per Lugano criteria.
  - Adverse events (graded by CTCAE version 5.0).
  - PK exposure parameters derived from plasma concentrations of AZD4205.
- [redacted]

[redacted]

Safety and tolerability, PK and biomarker data will be assessed as indicated in the table of assessments (Table 2 and Table 3), but may be adjusted based on emerging data during the study.

7.2 Determination of sample size

The objective of this study is to investigate the safety/tolerability, PK and anti-tumor efficacy of AZD4205 in patients with r/r PTCL. Hence the number of patients has been based on the desire to obtain adequate tolerability, safety, PK and biomarker data while exposing as few patients as possible to the investigational product and procedures.

Approximately 40 patients will be enrolled into two dose escalation cohorts in Part A dose escalation, including, 150 mg and 250 mg, with ~20 patients in each dose cohort. Approximately

10~20 additional patients are planned to be enrolled into an extension cohort in Part A and receive AZD4205 at selected dose in a single capsule dosage form.

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

7.3 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs, ECG changes. These will be collected for all patients. Appropriate summaries of these data will be presented.

ECG Changes

Immediate clinical management of patients will be done according to local assessment of the QT interval. For the Clinical Study Report QTc will be calculated using Fridericia's formula:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Creatinine Clearance

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

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

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

7.4 Calculation or derivation of PK variables

A 5-min window will be allowed for samples taken at 0.5 h and 1 h; a 10-min window for samples taken at 1.5-10 h; a 15-min window for samples taken at pre-dose; a 1-h window for samples taken at 24 h;

The timing of the PK samples may be adjusted during the study, depending on emerging data, in order to ensure appropriate characterization of the time profiles of plasma concentration. In order to monitor potential drug-drug interactions while the patients are taking some concomitant medications, additional blood samples may be collected and assayed for AZD4205, e.g. pre-dose and 4 h post-dose of the day by when the drug concentrations are presumed to reach steady state. The decision to take additional PK samples will reside with the SRC.

If a patient misses any doses of AZD4205 within 3 days of PK sampling, please contact the Sponsor PK representative as to any effect on the changes required on the timing of the PK assessments. All other assessments, including laboratory safety assessments, vital signs and response assessment should continue to be performed as per study plan, relative to baseline assessments.

PK analysis of the plasma concentration data for AZD4205 will be performed by LC/MS.

The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard non-compartmental methods.

Where possible the following PK parameters will be determined for AZD4205.

Following the first dose of the study on day 1:

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

Following the multiple dose part of the study:

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

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

Additional PK parameters may be determined if deemed appropriate. If the plasma concentrations of AZD4205 metabolite(s) are measured, then appropriate PK parameters for the metabolite(s) will be determined and reported separately from CSR.

Results from identification and characterization of metabolites and/or drug related products performed on relevant plasma samples will be reported separately from the CSR.

The plasma concentration data for AZD4205 will also be analyzed using a population PK approach, which may include exploring the influence of covariates on PK, if the data allows. An PK/PD approach will be used to investigate the relationship between PK and selected primary, secondary and/or exploratory endpoints, where deemed appropriate. Results may be reported separately from the Clinical Study Report for the main study.

The data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK/PD methods. The results of any such analyses will be reported separately from the CSR.

7.5 Calculation or derivation of tumor response variables

Below efficacy parameters will be applied to the assessment of the anti-tumor efficacy of AZD4205 in r/r PTCL.

7.5.1 Objective response rate

The ORR is defined as the proportion of achieving either a PR or CR, according to the Lugano Classification for NHL (Cheson BD et al. 2014). In Part A, the ORR is assessed by investigators.

In Part B, the ORR will be assessed by both an IRC and investigators, while the results by IRC will be used as primary assessment for analysis of primary endpoint, and a concordance analysis will be performed to compare the results by IRC and investigators.

The response of the PTCL to treatment must be consistent with clinical guidelines (Cheson BD et al. 2014) as listed in Table 9.

Overall response assessments will include evaluation of physical exams, bone marrow assessments, and radiographic evaluations per the Schedule of Assessments (see Table 2 and Table 3). Patients who have signs and symptoms of progression outside of the scheduled assessment should be evaluated by the investigator with a physical exam and laboratory assessments to determine if disease progression is present. In the event disease progression is suspected due to physical examination or laboratory test, a CT and/or PET scan must be performed to confirm disease progression. If medically appropriate, it is recommended that uncertain disease progression should be confirmed by an alternative diagnostic imaging modality or biopsy, e.g. diagnostic quality CT/biopsy to confirm metabolic disease progression, or cytologic test to confirm malignant effusion.

7.5.2 Progression Free Survival

PFS is defined as the time from the date of first dosing until the date of objective disease progression as defined by Lugano classification or death (by any cause in the absence of progression) regardless of whether the patient discontinues the study treatments.

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable tumor response assessment.

Note: Symptomatic deterioration will not be regarded as a progression event.

7.5.3 Duration of Response

Duration of response is defined as the time from the date of first documented response until the date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the first visit response of PR or CR.

If a patient does not progress following a response, then their duration of response will use the PFS censoring time.

7.5.4 Time to Response

For patients with observed response, time to response (TTR) is defined as the time from the date of first dosing to the time of the initial response of PR or CR.

7.5.5 Change in tumor size

Tumor size is defined as SPD (the sum of the product diameters) of target lesions by Lugano classification. Percentage change in tumor size will be determined for patients with measurable

disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of TLs compared to baseline.

For further details see Appendix VI of this Clinical Study Protocol.

[redacted]

7.6 Analysis sets

The analysis of data will be based on different subsets according to the purpose of the analysis. Throughout the safety results sections, erroneously treated patients (e.g., those assigned to receive dose A who actually received dose B, those who failed to meet the selection criteria) will be accounted for in the actual dose group received.

Table 11 Analysis set definition

Analysis Set	Definition
All patients	All patients screened
Safety	All patients who received at least 1 dose of AZD4205
Pharmacokinetics	All dosed patients with at least one reportable AZD4205 plasma concentrations and no important adverse events or protocol deviations that may impact PK
Evaluable for CT-based response	All dosed retrospectively confirmed PTCL patients with baseline measurable disease using CT imaging
Evaluable for survival	All dosed retrospectively confirmed PTCL patients
[redacted]	

7.7 Statistical methods

Summary statistics will be presented by study cohort unless otherwise specified.

Demographic data

Demographic data will be summarized in the safety analysis set.

Characteristics of the patients, including medical history and disease characteristics at baseline will be listed for each patient and summarized.

Reasons for discontinuation of investigational product will be listed including the study day of treatment discontinuation and will be summarized. Concomitant medications will also be listed and summarized.

Exposure

Exposure data will be summarized in the safety analysis set.

Exposure to investigational product i.e., total amount of study drug received will be listed for all patients.

Total exposure (date of last dose minus date of first dose + 1) will be summarized by the following: mean, standard deviation, minimum, maximum, median and number of observations. In addition, the number and percentage of patients with at least one dose interruption/dose delay and at least one dose reduction will be presented separately for the initial period defined as 21 days of multiple dosing (Cycle 1) and for any time following this initial period of the study.

Safety

Safety data will be summarized in the safety analysis set.

At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

Data from all cycles of initial treatment will be combined in the presentation of safety data. AEs will be listed individually by patient and dose cohort. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose cohort. The number of patients experiencing AE will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade. The number and percentage of patients with adverse events in different categories (e.g., causally related, CTCAE Grade $\geq$ 3 etc.) will be summarized by dose cohort, and events in each category will be further summarized by MedDRA system organ class and preferred term, by dose group. SAEs will be summarized separately if a sufficient number occur.

Any AE occurring within the defined 28 days follow-up period after discontinuation of investigational product will be included in the AE summaries. Any adverse events in this period that occur after a patient has received further therapy for cancer (following discontinuation of investigational product) will be flagged in the data listings.

Hematology, clinical chemistry, vital signs, ECG data, Echo/MUGA data and pulmonary function test data will be listed individually by patient and suitably summarized. For all laboratory variables, vital signs and ECG data, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations will be used.

Details of any deaths will be listed for all patients.

Any qualitative assessments will be summarized for all patients using the number and proportion of patients with results of negative, trace or positive.

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.

Pharmacokinetics

This will be summarized in the PK analysis set.

Plasma concentrations of AZD4205 will be summarized by nominal sample time. Plasma concentrations and derived PK parameters will be summarized by dose cohort. Parameters following single and multiple dosing will be summarized separately. Plasma concentrations at each time point will be summarized according to dose cohort by the following summary statistics:

- The geometric mean (G_{mean}, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (CV, calculated as $100\sqrt{[exp(s2)-1]}$, where s is the standard deviation of the data on a log scale)
- G_{mean} ± standard deviation (calculated as exp[μ±s])
- Arithmetic mean calculated using untransformed data
- Standard Deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

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

- G_{mean}, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- CV, calculated as $100\sqrt{[exp(s2)-1]}$, where s is the standard deviation of the data on a log scale)
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for, R_{AC},:

- Arithmetic mean
- Standard deviation

- Minimum
- Maximum
- Number of observations

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

- Median
- Minimum
- Maximum
- Number of observations

Regression based diagnostic parameters will be listed only and not summarized.

The PK data for AZD4205 after the first dose and separately, at steady state will also be displayed graphically. Displays will include plasma concentration patient profiles (on the linear and log-scale) versus time and G_{mean} concentration (+/-standard deviation) versus time, stratified by dose cohort.

For Part A, scatter plots of PK parameters versus dose, or log-dose will also be considered following both single and multiple dose administration of AZD4205 to assess dose proportionality if there are more than 2 dose levels.

In a preliminary assessment of dose proportionality, log-transformed AUC and C_{max} parameter estimates will be examined using the Power Model:

$$\text{parameter} = e^{a}(\text{dose})^{b}$$

$$\text{i.e., } \log(\text{parameter}) = a + (b * \log(\text{dose}))$$

where a is the intercept, depending on patients, and b is the slope, measuring the extent of dose proportionality. Dose proportionality implies that b=1 and will be assessed by estimating b along with its confidence interval.

If there is evidence of departures from dose proportionality, log-transformed dose-normalized AUC and C_{max} of AZD4205 will be analyzed separately using a mixed effects model. Dose will be fitted as a fixed effect and patient as a random effect. Point estimates and associated 90% confidence intervals (CIs) for the differences between each dose level and the reference dose (the lowest dose) will be constructed using the residual variance. The estimates will then be back-transformed to provide point estimates and corresponding 90% CIs for the ratios of each dose level to the reference dose on the original scale. No adjustments for pre-planned multiple comparisons will be made. This analysis will only be performed provided there are sufficient data.

If only limited dose levels are being studied; i.e. no more than 2 dose levels, then the dose paranormality analysis using power model will not be useful and only box and whisker plots will be presented comparing the two dose levels for C_{max} and $AUC_{(0\text{-}24)}$.

Tumor response

The analysis population for best objective response will be all the evaluable patients for efficacy assessment. Objective response rate (ORR) will be valued based on Lugano criteria by dose cohort.

Summaries of the number of patients with best objective response in each cohort will be provided in the following categories: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) and Non-Evaluable (NE).

Patients in Part B who are not PTCL by retrospective histological confirmation will be excluded from efficacy analysis. The tumor response summaries will be provided by both IRC assessment-based and investigators assessment-based results. Tumor response in Part B will also be summarized by retrospective confirmed histological subtypes.

Duration of response

The analysis population for duration of response will be the subset of the evaluable for response population with a best overall response of CR/PR. A Kaplan Meier plot and median duration of response (calculated from the Kaplan-Meier) will be presented.

Time to response

The analysis population for duration of response will be the subset of the evaluable for response population with a best overall response of CR/PR. A Kaplan Meier plot and median duration of response (calculated from the Kaplan-Meier) will be presented.

Change in tumor size

The analysis population for change in tumor size will be the evaluable response populations. Patients without observed or imputed post baseline target lesion measurements for the visit of interest will be excluded.

The absolute values and percentage change in target lesion tumor size from baseline will be summarized using descriptive statistics and presented at each time point. Best change will also be summarized.

Tumor size will also be presented graphically using waterfall plots, presenting each patient's percentage change in tumor size as a separate bar. If PET status is used to designate a CR (i.e. PR with negative PET), then these patients should be identified by a separate color of the bars, or by an asterisk in a waterfall plot.

Progression free survival

The analysis populations for PFS will be the evaluable for survival analysis set.

In Part B, PFS will be displayed using a Kaplan-Meier plot. The number of events, median (calculated from the Kaplan-Meier plot) will be summarized.

[redacted]

[redacted]

8. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

8.1 Medical emergencies and Sponsor contacts

The Principal Investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes a SAE and is to be reported as such, see Section 6.5.4.

In the case of a medical emergency the investigator may contact the Study Physician. If the Study Physician is not available, contact the Study Leader at Sponsor Research and Development.

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

8.2 Overdose

Overdose of AZD4205

There are no data on overdosing of AZD4205 at present. There is no known antidote. Investigators will be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

Such overdoses should be recorded as follows:

• An overdose with associated AEs/SAEs is recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the CRF and on the overdose CRF module.

• An overdose with no associated symptoms is only reported on the overdose CRF module.

If an overdose occurs in the course of the study, then investigators or other site personnel inform appropriate Sponsor representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the Sponsor Patient Safety data entry site.

For overdoses associated with a SAE, standard reporting timelines apply, see Section 6.5.4. For other overdoses, reporting should be done within 28 days.

8.3 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to Sponsor using the appropriate forms.

8.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of a pregnancy should be followed up and documented even if the patient was withdrawn from the study.

If a pregnancy occurs during exposure to investigational product or in the 28 days after discontinuing investigational product, then investigators or other site personnel inform appropriate Sponsor representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the Sponsor Patient Safety data entry site within 1 or 5 days for SAEs, (see Section 6.5.4) and within 28 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.3.2 Paternal exposure

Pregnancy of a patient's partner is not considered to be an adverse event. However, any conception occurring from the date of dosing until 16 weeks after dosing should be reported to Sponsor and followed up for its outcome.

9. PUBLICATION POLICY

The investigational sites may publish or present the results of this study under an agreement with the Sponsor. The Sponsor will be furnished with a copy of any proposed publication or presentation at least 2 weeks prior to submission. Upon notice by the Sponsor, however, that the Sponsor reasonably believes that a patent application claiming an invention related to the study drug generated during the study will be filed prior to such publication, such publication may be delayed for some time or until any patent application or applications have been filed, whichever will first occur.

10. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

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 (e.g., 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 patients.
- Dizal will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a third party, but the accountability remains with Dizal.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - 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 patients 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 utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure or state other documents and will notify the IRB/IEC, if appropriate according to local requirements.

Financial Disclosure

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.

Informed Consent Process

- Include the primary ethical concerns of this study. Consider the key elements of the informed consent process, including any special concerns and how addressed (e.g., assent, capacity, legally acceptable representative).
- The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized 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 center.

- 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 authorized person obtaining the informed consent must also sign the ICF.
- Patients 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 patient or the patient's legally authorized representative.

Data Protection

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient 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 must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Dissemination of Clinical Study Data

A description of this clinical study will be available on 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 main study is conducted.

Data Quality Assurance

- All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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 (e.g., 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 (e.g., Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator after study completion per site contract 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.

Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF 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.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients 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.

Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the screening of the first patient 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment (evaluated after a reasonable amount of time) of patients by the investigator
- Total number of patients included earlier than expected

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 organization(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 patient and should assure appropriate patient therapy and/or follow-up.

Table 12 Lab visit and clinical monitoring schedule

	Screening		C1D1		C1D8		C1D15		C2D1		C3D1		C4D1		C5D1 onwards D1		End of treatment	
		Blood Volume		Blood Volume		Blood Volume		Blood Volume		Blood Volume		Blood Volume		Blood Volume		Blood Volume		Blood Volume
Part A: Dose escalation and extension cohorts																		
Hematology	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml
Serum chemistry	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml
Coagulation	×	2ml	×	2ml	×	2ml	×	2ml	×	2ml	×	2ml	×	2ml	×	2ml	×	2ml
HBV, HCV, HIV screening	×	6ml																
Urinalysis	×		×		×		×		×		×		×		×		×	
Pregnancy Test (Urine)	×		×														×	
Plasma PK PRE			×	2ml	×	2ml	×	2ml	×	2ml	×	2ml	×	2ml				
Plasma PK 0.5HR POST			×	2ml					×	2ml								
Plasma PK 1HR POST			×	2ml					×	2ml								
Plasma PK 1.5HR POST			×	2ml					×	2ml								
Plasma PK 2HR POST			×	2ml					×	2ml								
Plasma PK 2.5HR POST			×	2ml					×	2ml								
Plasma PK 3HR POST			×	2ml					×	2ml								
Plasma PK 4HR POST			×	2ml					×	2ml								
Plasma PK 6HR POST			×	2ml					×	2ml								
Plasma PK 8HR POST			×	2ml					×	2ml								
Plasma PK 10HR POST			×	2ml					×	2ml								
Plasma PK 24HR POST			×	2ml					×	2ml								
pSTATs PRE [A]			×	6ml			×	6ml										
pSTATs 2H POST [A]			×	6ml														

Table 12 Lab visit and clinical monitoring schedule

	Screening		C1D1		C1D8		C1D15		C2D1		C3D1		C4D1		C5D1 onwards D1		End of treatment	
		Blood Volume		Blood Volume		Blood Volume		Blood Volume		Blood Volume		Blood Volume		Blood Volume		Blood Volume		Blood Volume
pSTATs 24H POST [A]			×	6ml														
Blood for mutation detection	×	12ml																
Bone marrow aspiration for tumor response assessment [B]	×																	
BP/HR	×		×	PRE, 1,2,4,8,24 POST	×	PRE	×	PRE	×	PRE, 1,2,4,8 POST	×		×		×		×	
ECG	×		×	PRE, 1,2,4,8,24 POST	×	PRE	×	PRE	×	PRE, 1,2,4,8 POST	×		×		×		×	
Total		28ml		52ml		12ml		18ml		34ml		12ml		12ml		10ml		10ml
Part B: Dose expansion cohort																		
Hematology	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml
Serum chemistry	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml	×	4ml
Coagulation	×	2ml	×	2ml	×	2ml	×	2ml	×	2ml	×	2ml	×	2ml	×	2ml	×	2ml
HBV, HCV, HIV screening [C]	×	6ml																
Urinalysis	×		×		×		×		×		×		×		×		×	
Pregnancy Test (Urine)	×		×														×	
Plasma PK PRE [D]			×	2ml				2ml	×	2ml			×	2ml				
Plasma PK 1HR POST [D]			×	2ml					×	2ml								
Plasma PK 2HR POST [D]			×	2ml					×	2ml								
Plasma PK 4HR POST [D]			×	2ml					×	2ml								
Plasma PK 6HR POST [D]			×	2ml					×	2ml								
Plasma PK 8HR POST [D]			×	2ml					×	2ml								
Plasma PK 24HR POST [D]			×	2ml					×	2ml								

Table 12 Lab visit and clinical monitoring schedule

	Screening		C1D1		C1D8		C1D15		C2D1		C3D1		C4D1		C5D1 onwards D1		End of treatment	
		Blood Volume		Blood Volume		Blood Volume		Blood Volume		Blood Volume		Blood Volume		Blood Volume		Blood Volume		Blood Volume
pSTATs PRE [A]			×	6ml			×	6ml										
pSTATs 2H POST [A]			×	6ml														
pSTATs 24H POST [A]			×	6ml														
Blood sample for pharmacogenetics research[E]	×	10ml																
Bone marrow aspiration for tumor response assessment [B]	×																	
BP/HR	×		×	PRE, 1,2,4,8 POST	×	PRE	×	PRE	×	PRE, 1,2,4,8 POST	×		×		×		×	
ECG	×		×	PRE, 1,2,4,8 POST	×	PRE	×	PRE	×	PRE, 1,2,4,8 POST	×		×		×		×	
Total		26ml		42ml		10ml		18ml		24ml		10ml		12ml		10ml [F]		10ml

Footnote:

A. Blood sampling for pSTATs inhibition of blood cells is only mandatory for patients enrolled in the designated sites.

B. During the treatment, bone marrow aspiration/biopsy will be performed when a complete response needs to be confirmed and when clinically indicated.

C. Both HBsAg and HBcAb should be negative for eligibility.

D. In part B, patients at the selected sites will be invited for intense PK study on Cycle 1 Day 1 and Cycle 2 Day 1.

E. Blood samples for pharmacogenetics research at screening are optional for patients enrolled in the part B.

F. Total 12 ml blood on Cycle 6 Day 1 (Part B), because of pre-dose PK sampling on C6D1.

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APPENDIX I. HEART FUNCTION BY NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath). Patient has no symptoms when walking, climbing stairs, etc.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath) or angina.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity (e.g. walking short distance 20-100m) causes fatigue, palpitation, dyspnea or angina.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

APPENDIX II. GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

The use of any natural/herbal products or other "folk remedies" (e.g. Ginseng and other Traditional Chinese Medicine) should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

AZD4205 is an investigational drug for which no data on *in vivo* interactions are currently available in human. Based on *in vitro* data and predicted clinical exposure data, AZD4205 is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity.

In vitro data have shown that the principal CYP enzymes responsible for the Phase I metabolism of AZD4205 is CYP 3A4. Therefore, drugs strongly inhibiting CYP3A4/5 metabolism are recommended not to combine with AZD4205. Drugs inducing CYP3A4/5 metabolism should also be avoided to combine with AZD4205 if possible.

During the treatment of AZD4205, live vaccines should be avoided.

Drugs inhibiting CYP3A4/5 metabolism that Sponsor recommend are not combined with AZD4205.

The contribution of Phase I metabolism to the total clearance of AZD4205 is currently unknown but, to ensure patient safety, the following potent inhibitors of CYP3A4/5 must not be used during this study for any patient receiving AZD4205.

Table A1. Drug inhibiting CYP3A4/5

Contraindicated drugs	**Withdrawal period prior to AZD4205 start**
Ketoconazole, itraconazole, indinavir, saquinovir, nelfinavir, atazanavir, amprenavir, fosamprenavir, troleandomycin, telithromycin, fluconazole, nefazodone, cimetidine, aprepitant, miconazole, fluvoxamine	1 week
Amiodarone	27 weeks
Erythromycin, clarithromycin, verapamil, ritonavir, diltiazem	2 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4/5 activity. Appropriate medical judgment is required. Please contact Sponsor with any queries you have on this issue.

Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits, e.g., grapefruit juice or marmalade) during the study because of inhibition of intestinal CYP3A4 metabolism, e.g. no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1 to 2 teaspoons (15 g) of Seville orange marmalade daily.

Drugs inducing CYP3A4 metabolism that Sponsor recommend are not combined with AZD4205

To avoid potential reductions in exposure due to drug interactions, the following CYP3A4/5 inducers should be avoided if possible.

Table A2. Drug inducing CYP3A4/5

Contraindicated drugs	Withdrawal period prior to AZD4205 start
Phenytoin, rifampicin, St. John's Wort, carbamazepine, primidone, griseofulvin, barbiturates, troglitazone, pioglitazone, oxcarbazepine, nevirapine, efavirenz, rifabutin	3 weeks
Phenobarbitone	5 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4/5 activity. Appropriate medical judgment is required. Please contact Sponsor with any queries you have on this issue.

Additional guidance for drugs whose exposure may be affected by AZD4205

In vitro data suggests that AZD4205 has weak inhibition on the drug transporters including P-gp, OAT1 and OAT3 (IC_{50} >100 μM), and moderate inhibition on BCRP, OATP1B1, OCT2, MATE1 and MATE2-K (IC_{50}s of 37.1, 47.4, 10.2, 0.725 and 0.739 μM, respectively). Exposure of those co-medications whose disposition depends on kidney OCT2, MATE1 and MATE2-K could be altered. DDI risk via inhibition of intestinal CYP3A4 metabolism and BCRP efflux and hepatic OATP1B1 uptake could not be ruled out. Thus, co-medication whose disposition/elimination mainly depends on these transporters with narrow therapeutic index and drug related safety events should be closely monitored following the recommendation from drug label.

Table A3. Exposure, pharmacological action and toxicity that may be increased by AZD4205

	Warning of possible interaction and corresponding advices
Rosuvastatin Pravastatin Pitavstatin Atorvastatin Simvastatin Fluvastatin	These drugs are permitted but caution should be exercised. It is recommended that the starting and maintenance dose should be as low as possible and should be guided by the drug label. In addition, the times of administration of the statins and/or ezetimibe and AZD4205 should be staggered such that the maximum levels of both drugs in the gut do not coincide. For patients receiving these drugs, additional monitoring of low-density lipoprotein (LDL) cholesterol levels and liver enzymes is advised. If the patient experiences any potentially relevant adverse events suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, the lipid-lowering treatment should be stopped and creatine kinase (CK) levels should be checked, and any appropriate further management should be taken.
Metformin	Active secretion via kidney transporters are highly involved for metformin elimination, thus inhibition of these transporters has the potential to interfere with the transport of metformin and ultimately affect both plasma and intracellular concentrations of metformin. Lactic acidosis, a rare but serious complication, can occur due to metformin accumulation. Thus, metformin is permitted with cautions. Please follow the recommendation stated in metformin label. If patients experience any potentially relevant adverse events as metformin label, metformin associated lactic acidosis tests should be check and metformin treatment should be stopped to follow metformin drug label.

Drugs that may prolong QT interval

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland. Ref: http://www.arizonacert.org/medical-pros/drug-lists/druglists.htm.

Drugs known to prolong QT interval

The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with AZD4205. Recommended withdrawal periods following cessation of treatment with these agents are provided in the table below

Table A4. Drugs prolonging QT interval

Contraindicated drug	Withdrawal period prior to AZD4205 start
Clarithromycin, droperidol, erythromycin, procainamide	2 days

Cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine	7 days
Bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine	14 days
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide	6 weeks*
Pentamidine	8 weeks
Amiodarone, chloroquine	1 year

* Estimated value as PK of arsenic trioxide has not been studied

Drugs that may possibly prolong QT interval

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated.

Table A5. Drugs that may possibly prolong QT interval

Contraindicated drug	**On treatment duration prior to AZD4205 start**
Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, foscarnet, galantamine, gemifloxacin, isradipine, ketoconazole, levofloxacin, mexiletine, nicardipine, octreotide, ofloxacin, ondansetron, quetiapine, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine, ziprasidone	2 days
Amantadine, amitriptyline, amoxapine, clozapine, doxepin, felbamate, flecainide, fluconazole, fosphenytoin, gatifloxacin, granisetron, imipramine, indapamide, lithium, moexipril/HCTZ, moxifloxacin, risperidone, roxithromycin, sertraline, trimethoprin-sulfa, trimipramine, voriconazole	7 days
Azithromycin, citalopram, clomipramine, itraconazole, nortriptyline, paroxetine, solifenacin, tacrolimus	14 days
Fluoxetine	5 weeks
Protriptyline	6 weeks
Tamoxifen	8 weeks

APPENDIX III. HY'S LAW

Introduction

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Sponsor clinical project representatives, 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 other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) $\geq 3 \times$ Upper Limit of Normal (ULN) and Total Bilirubin (TBL) $\geq 2 \times$ ULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT $\geq 3 \times$ ULN and TBL $\geq 2 \times$ ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

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 patient who meets any of the following identification criteria in isolation or in combination:

- ALT $\geq 3 \times$ ULN
- AST $\geq 3 \times$ ULN
- TBL $\geq 2 \times$ ULN

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

- Notify the Sponsor representative

- Determine whether the patient meets PHL criteria (see Section Definitions of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases (See Section Actions required when potential Hy's law criteria are met before and after starting study treatment).
- Notify the Sponsor representative who will then inform the central Study Team.

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the three Liver CRF Modules as information becomes available.
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

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.

No later than 3 weeks 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 other than DILI caused by the IMP. The Sponsor Medical Science Director 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.

If 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 CRF.
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the Dizal standard processes.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to Sponsor standard processes.
- The 'Medically Important' serious criterion should be used if no other serious criteria apply.
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above.
- 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 met. Update the SAE report according to the outcome of the review.

Actions required when potential Hy's law criteria are met before and after starting study treatment

This section is applicable to patients 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, even if there has been no significant change the patient's condition# compared with pre-study treatment visits, the Investigator will:

- Notify the Sponsor representative who will inform the central Study Team.
- Follow the subsequent process described is Section Potential Hy's Law Criteria met of this Appendix.

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether

there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

Actions required for repeat episodes of potential Hy's law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

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 chronic or progressing malignant disease or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section Actions required when potential Hy's law criteria are met before and after starting study treatment?

If No: follow the process described in Section Potential Hy's Law Criteria met of this Appendix

If Yes:

Determine if there has been a significant change in the patient'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 Potential Hy's Law Criteria met of this Appendix.

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

APPENDIX IV. FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening:** Refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe (e.g., hepatitis that resolved without hepatic failure).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization:** Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
- Results in **persistent or significant disability or incapacity**.
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. 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, hospitalization, disability or incapacity but may jeopardize the patient or may require medical intervention 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 should be used.

  Examples of such events are:

  - 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 (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization.
  - Development of drug dependency or drug abuse.

A guide to interpreting the causality QUESTION

The following factors should be considered 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 patient 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 etiology 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? Sponsor would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any de-challenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

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

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

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

APPENDIX V. INTERNATIONAL AIRLINE TRANSPORTATION ASSOCIATION (IATA) 6.2 GUIDANCE DOCUMENT

Labelling and Shipment of Biohazard Samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

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 e.g. Ebola, Lassa fever virus

- are to be packed and shipped in accordance with IATA Instruction 602

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g. Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging.
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

APPENDIX VI. RECOMMENDATIONS FOR INITIAL EVALUATION, STAGING, AND RESPONSE ASSESSMENT OF HODGKIN AND NON-HODGKIN LYMPHOMA: THE LUGANO CLASSIFICATION

1. Introduction

This appendix details the implementation of the 2014 Lugano classification (Cheson BD et al. 2014) for the AZD4205 study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study.

The PTCL tumor burden and response assessment will be performed and conducted based on comprehensive analysis of patients' CT scans (with contrast unless contraindicated), FDG-PET (where available) and bone marrow aspiration/biopsy. The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits. Specific time point and frequency of tumor burden and response assessment would be found in study visit schedule (Table 2 and Table 3).

2. CT-based Tumor Response Assessment

All patients will be required to receive CT-based tumor response assessment according to the study plan (Table 2 and Table 3). The CT-based tumor response assessment should be performed based on contrast CT scans (unless contraindicated), including neck, chest, abdomen, and pelvis and any other disease sites suspected by signs and symptoms.

Baseline assessment:

The CT scans for baseline tumor assessment should be performed within 28 days prior to (preferably close to) the first dose of study treatment. Investigators or independent review committee should identify lymphomatous lesion sites based on radiological imaging according to the criteria listed in Table 13.

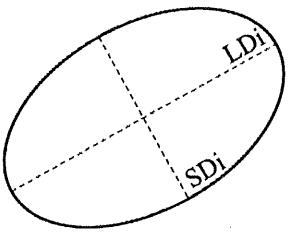
Table 13 Criteria for Involvement of Site

Site	Clinical	FDG Avidity	Test	Positive Finding
Lympho nodes	Palpable	FDG-avid histologies	PET	Increased FDG uptake
		Nonavid disease	CT	Unexplained node enlargement
Spleen	Palpable	FDG-avid histologies	PET	Diffuse uptake, solitary mass, miliary lesions, nodules
		Nonavid disease	CT	>13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies	PET	Diffuse uptake, mass
		Nonavid disease	CT	Nodules
CNS	Signs, symptoms		CT	Mass lesion(s)
			MRI	Leptomeningeal infiltration, mass lesions
			CSF	Cytology, flow cytometry
Other	Site dependent		PET, biopsy	Lymphoma involvement

The baseline CT-based tumor assessment includes four aspects:

Target lesions: Up to six of the largest measurable lymphomatous nodes/nodal masses/other lymphomatous lesions should be identified as target lesion(s) from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved.

- Measurable lesion refers to lymphomatous node/nodal masses/other lymphomatous lesions that are measurable in two diameters including longest diameter (LDi) and shortest diameter (shortest axis perpendicular to the LDi, SDi) on CT scans (with contrast unless contraindicated). A measurable node must have an LDi greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm.



- No concurrent or prior radiotherapy to target lesions are allowed.
- The SPD (sum of the product of the perpendicular diameters) of target lesion(s) needs to be calculated at each response assessment visit (at baseline and during follow-up visits).

Non-measured lesions: All other lymphomatous lesions should be followed as non-measured lesions, including unmeasurable lymphomatous lesions (e.g. pleural), unconfirmed lymphomatous lesions, and the measurable lesions that are not selected as target lesions.

- Palliative radiotherapy to pre-existing stable sites of non-measured lesions is allowed.
- In patients in whom a discordant histology or malignant transformation is suspected, a PET-CT may identify the optimal site to biopsy for confirmation.

Organ enlargement: Assess splenic size for involvement by vertical (cranial to caudal) length, > 13 cm is considered involved. However, a spleen may be of normal size and still contain lymphoma or maybe enlarged as a result of variations in blood volume, use of hematopoietic growth factors, or lymphoma unrelated causes. Splenic involvement is best determined by PET/CT and may be characterized by homogeneous splenomegaly, diffuse infiltration with miliary lesions, focal nodular lesions, or a large solitary mass. Splenic nodules may be selected as target lesions if they meet measurable criteria.

- Given variability in body habitus and the impact of numerous medical conditions, liver size by physical examination or CT scan is not a reliable measure of hepatic involvement by lymphoma. Similar to splenic involvement, diffusely increased or focal uptake, with or without focal or disseminated nodules, supports liver involvement. Hepatic nodules may be selected as target lesions if they meet measurable criteria.

Bone marrow involvement: In this study, the bone marrow involvement status should be confirmed based on bone marrow aspiration/biopsy. A bone marrow aspirate and biopsy should be done at screening.

Tumor response assessment (CT-based)

During the study treatment, CT scans of the same sites with screening should be performed for tumor response assessments within 7 days of Day 1 of Cycle 3, 6, 9 and then every three cycles

until confirmed disease progression, death or withdraw from the study. For patients with confirmed bone marrow involvement at baseline, if complete remission is suspected based on radiological imaging, the bone marrow aspiration/biopsy should be done at the same visit to confirm the involvement status. Clinical response of progressive disease (PD), stable disease (SD), partial response (PR), or complete response (CR) should be determined at each assessment according to 2014 Lugano classification (see Table 9).

Any patient who discontinues study treatment for reasons other than disease progression should have response assessment performed as scheduled in the protocol until disease progression or death occurs, unless consent is withdrawn.

Table 14 CT-based response categories per 2014 Lugano classification

Response	Site	CT-based response criteria
Complete response	Target lesion(s)	All of the following: - Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi - No extra-lymphatic sites of disease
	Non-measured lesion(s)	Absent
	Organ enlargement	Regress to normal
	New lesion(s)	None
	Bone marrow	Normal by morphology; if indeterminate, IHC negative
Partial response	Target lesion(s)	All of the following: - ≥ 50% decrease in SPD of up to 6 target lesions - When a lesion is too small to measure on CT, assign 5 mm ×5 mm as the default value - When no longer visible, 0 mm × 0 mm - For a node > 5 mm × 5 mm, but smaller than the normal, use actual measurement for calculation
	Non-measured lesion(s)	Absent/normal, regressed, but no increase
	Organ enlargement	Spleen must have regressed by > 50% in length beyond normal
	New lesion(s)	None
	Bone marrow	Not applicable
Stable disease	Target lesion(s)	< 50% decrease from baseline in SPD of up to 6 target lesions; no criteria for progressive disease are met
	Non-measured lesion(s)	No increase consistent with progression
	Organ enlargement	No increase consistent with progression
	New lesion(s)	None
	Bone marrow	Not applicable
Progressive disease	Target lesion(s)	Progressive disease requires at least 1 of the following: - An individual node/lesion must be abnormal with: o LDi > 1.5 cm and o Increase by ≥ 50% from PPD nadir and o An increase in LDi or SDi from nadir ▪ 0.5 cm for lesions ≤ 2cm ▪ 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 (e.g., 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

Response	Site	CT-based response criteria
	Non-measured lesion(s)	New or clear progression of preexisting non-measured lesions
	New lesion(s)	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent involvement

Footnote:
Abbreviations: CT, computed tomography; GI, gastrointestinal; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; 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.
* Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two 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 (e.g., liver, spleen, kidneys, and 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 extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.

Nodes or Extranodal Lesions That Split When Disease Is Responding

If a confluent nodal mass splits into several discrete nodes, the individual product of the perpendicular diameters (PPDs) of the nodes should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression (as if each individual node was selected as a target lesion at baseline).

Nodes or Extranodal Lesions That Become Confluent When Disease Is Progressing

If a group of target lymph nodes becomes confluent, the PPD of the current confluent mass should be compared with the sum of the PPDs of the individual nodes, with more than 50% increase in the PPD of the confluent mass compared with the sum of individual nodes necessary to indicate progressive disease. The LDi and shortest diameter are no longer needed to determine progression.

3. PET-based Tumor Response Assessment

At present, FDG-PET is generally accepted as one of preferred procedures for the clinical staging of lymphoma, especially for the FDG-avid disease. The PET-based tumor response is commonly assessed using a semi-quantiative methord called Deauville five-point scale (5-PS, see Table 15). 5-PS is based on visual interpretation of FDG uptake, and takes advantage of two reference points of individual patient, which have demonstrated relatively constant uptake on serial imaging. The two reference organs are mediastinum and liver.

Table 15 5 - POINT SCALE (5-PS)

Score 1	No uptake above background
Score 2	Uptake ≤ mediastinum
Score 3	Uptake > mediastinum, but ≤ liver
Score 4	Uptake moderately > liver
Score 5	Uptake markedly higher than liver and/or new lesions
X	(New) areas of uptake unlikely to be related to lymphoma

For patients with PET-avid disease at baseline, PET is recommended to be performed, where available, on Day 1 of Cycle 3 and when clinically need to confirm a complete response. Patients with confirmed CR are not required to undergo further PET/CT scans on study unless there is suspicion of progressive disease.

If disease is confirmed to be not PET-avid at baseline, restage assessments could be performed using CT scans of diagnostic quality.

NOTE: PET/CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality, adheres to the specified slice thickness/scan parameters, and includes the use of IV contrast. Also, the CT images must be separated from the PET data prior to submitting the data, and cannot be transmitted as fused CT/PET images.

The response of the patient's PTCL to treatment must keep consistent with clinical guidelines (Cheson BD et al. 2014) as listed in Table 16.

Table 16 PET-based response categories per 2014 Lugano classification

Response	Site	PET-based response criteria
Complete metabolic response	Target lesion(s)	Score 1, 2, or 3* with or without a residual mass on 5 point scale (5-PS)
	Non-measured lesion(s)	Not applicable
	Organ enlargement	Not applicable
	New lesion(s)	None
	Bone marrow	No evidence of FDG-avid disease in the marrow
Partial metabolic response	Target lesion(s)	Score 4 or 5 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
	Non-measured lesion(s)	Not applicable
	Organ enlargement	Not applicable
	New lesion(s)	None
	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

Response	Site	PET-based response criteria
No metabolic response	Target lesion(s)	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment
	Non-measured lesion(s)	Not applicable
	Organ enlargement	Not applicable
	New lesion(s)	None
	Bone marrow	No change from baseline
Progressive metabolic disease	Target lesion(s)	Score 4 or 5 with increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment
	Non-measured lesion(s)	None
	New lesion(s)	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered
	Bone marrow	New or recurrent FDG-avid foci

Footnote:
Abbreviations: 5PS, 5-point scale; FDG, [^{18}F]fluorodeoxyglucose; GI, gastrointestinal; MRI, magnetic resonance imaging; PET, positron emission tomography.
*A score of 3 in many patients 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 undertreatment). In Waldeyer's ring or in extranodal sites (e.g., 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 (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

4. Additional Response Assessment Guidelines

Patients who have signs and symptoms of progression outside of the scheduled assessment should be evaluated by the investigator with a physical exam and laboratory assessments to determine if disease progression is present. In the event disease progression is suspected due to physical examination or laboratory test, a CT and/or PET scan must be performed to confirm disease progression. If medically appropriate, it is recommended that uncertain disease progression should be confirmed by an alternative diagnostic imaging modality or biopsy, e.g. diagnostic quality CT/biopsy to confirm metabolic disease progression, or cytologic test to confirm malignant effusion.

The presence of residual symptoms in the absence of detectable disease by imaging does not preclude the designation CR. In the context of an agent associated with a flare reaction, caution must be exercised not to confuse the possible tumor flare with progressive disease. It is recommended that either a biopsy be performed or the lesion be reassessed in at least 2 weeks, and if there is continued evidence of tumor progression, the date of progressive disease is the previous evaluation.

5. References

Cheson BD et al. 2014

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification [J]. Journal of Clinical Oncology, 2014, 32(27).

APPENDIX VII. GUIDANCE FOR THE SAFETY MONITERING AND MANAGEMENT OF ADVERSE EVENTS

1. Introduction

AZD4205 is a potent, oral, ATP-competitive inhibitor of JAK1 kinase. It is intended for the treatment of advanced cancer patients as monotherapy in this study.

Whilst there is no clinical experience with AZD4205, preclinical studies suggest a potential association between the use of AZD4205 and adverse events of cardiac, liver, lung etc. been observed. When the appropriate treatment of these events is instituted, they can be tolerable, allowing patients to continue receiving treatment.

The purpose of these treatment guidelines is:

- To prevent tolerable adverse events becoming intolerable for the patient and leading to discontinuation of treatment.
- To promote consistency of monitoring and treatment for specific adverse events across the AZD4205 clinical development program.

2. Cardiovascular Effects

Whilst there is no clinical experience with AZD4205, preclinical studies suggest a potential association between the use of AZD4205 and the occurrence of cardiovascular events has been observed. As a result, sponsor has chosen to include Digital ECG, Echo/MUGA (multigated acquisition scan) and highly-sensitive Troponin T and NT-pro BNP levels in the clinical safety monitoring.

It is important that patients are fully informed that potential cardiac events may occur during treatment with AZD4205.

Safety monitoring with ECGs:

- Twelve-lead triplicate ECG will be performed at the visit indicated in the Study Plan.
- A standardized ECG machine should be used, and the patient should be examined using the same machine throughout the study.
- The digital ECGs should be analyzed by an ECG Central lab.
- Single ECGs should also be performed at the time of significant LVEF drop and on occurrence of any cardio-respiratory adverse event of non-obvious cause (obvious causes will be managed in accordance with local clinical practice). For patients with new or worsening respiratory symptoms (such as dyspnea, cough), an ECG is recommended and additionally at the discretion of the investigator if clinically indicated.
- During the study, clinically significant abnormal ECG findings not present at baseline should be reported as an AE. It is recommended that asymptomatic ECG findings should be adjudicated by an expert reader if case they are reported as AEs. If present, the clinical signs

and symptoms associated with the abnormal finding should be reported as the AE with the ECG abnormality given as explanatory information.

- Management of QTc prolongation: A QTcF > 500 ms is an independent criterion for individual pro-arrhythmic risk. Any QTcF > 500 ms should trigger a repeat ECG timepoint in 5-10 min to confirm the finding. If confirmed, patient will be withdrawn from study Patients experiencing QTc interval prolongation with signs/symptoms of serious arrhythmia will not be permitted to restart study treatment.

Safety monitoring with Echocardiogram/MuGA:

- The modality of the cardiac function assessments must be consistent within a patient i.e. if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans.
- The patients should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken. Recommendations include having complete high quality standardized 2-D with Doppler echocardiographic examinations performed by an experienced sonographer and include evaluation of both systolic and diastolic left ventricular function.
- Ejection fraction determinations should be determined quantitatively based on bi-plane measurements of end diastolic and end systolic left ventricular volumes.
- Any **symptomatic** decrease in LVEF will prompt the discontinuation of the treatment and a cardiac consultation.
- Below table is the reference for the management of asymptomatic decrease of LVEF:

Absolute EF	Decrease from Baseline <10%	Decrease from Baseline 10-15%	Decrease from Baseline >15%
55% or above	Continue	Continue	Interruption*. ECHO/MUGA in 3 weeks. If value back to baseline, consider dose resumption.
54-40%	Continue	Interruption. Cardiac consultation. ECHO/MuGA in 3 weeks. If LVEF above 55% consider dose resumption	Discontinue. Cardiac consultation
Below 40%	Interruption. Cardiac consultation	Discontinue. Cardiac consultation	Discontinue. Cardiac consultation

Footnote: *A subject with EF decreasing by > 15% and remaining > 55% would have to start from > 70%, i.e. a very high normal. Hypovolemia, hyperthyroidism and hypertrophic/constrictive/significant restrictive cardiomyopathy should be considered and ruled out.

Troponin and NT-pro BNP

- Both high sensitivity troponin T testing (TnT or hs-TnT) and NT-pro BNP will be performed.
- A core/central laboratory is recommended to ensure that the same assay is used for a given study and, if feasible, for all studies in the same program to minimize systematic errors. When using a central laboratory, if a local laboratory is used for ad hoc cTn testing for the purpose of patient management, a duplicate sample should be sent to the core/central laboratory whenever possible.
- When clinically indicated by unexpected significant TnT rise, a TnT sample should be repeated and evaluation by ECHO considered. When indicated by symptoms and signs of suspected ischemic event, an increased TnT should trigger TnT sampling schedule. If there is an unexpected rise in cTnT, additional time points are needed to capture the time course of the cTnT changes, repeating the test at appropriate intervals. A core laboratory should be utilized to ensure the same assay is used in the study.
- It was not suggested to give a specific exclusion or discontinuation cut-off values for TnT in patients without symptoms or signs of unstable ischemic cardiac disease or progressing symptomatic congestive heart failure.

Referral to cardiologist

- Patients experiencing QTc interval prolongation with signs/symptoms of serious arrhythmia should be referred to cardiologist.
- Cardiologist examination findings should be documented in the patient's notes and reported to sponsor if required.
- In addition, a report should be provided to sponsor detailing:
  - Cardiologist examination performed.
  - Findings or change from baseline
- Treatment administered should be captured on the CRF

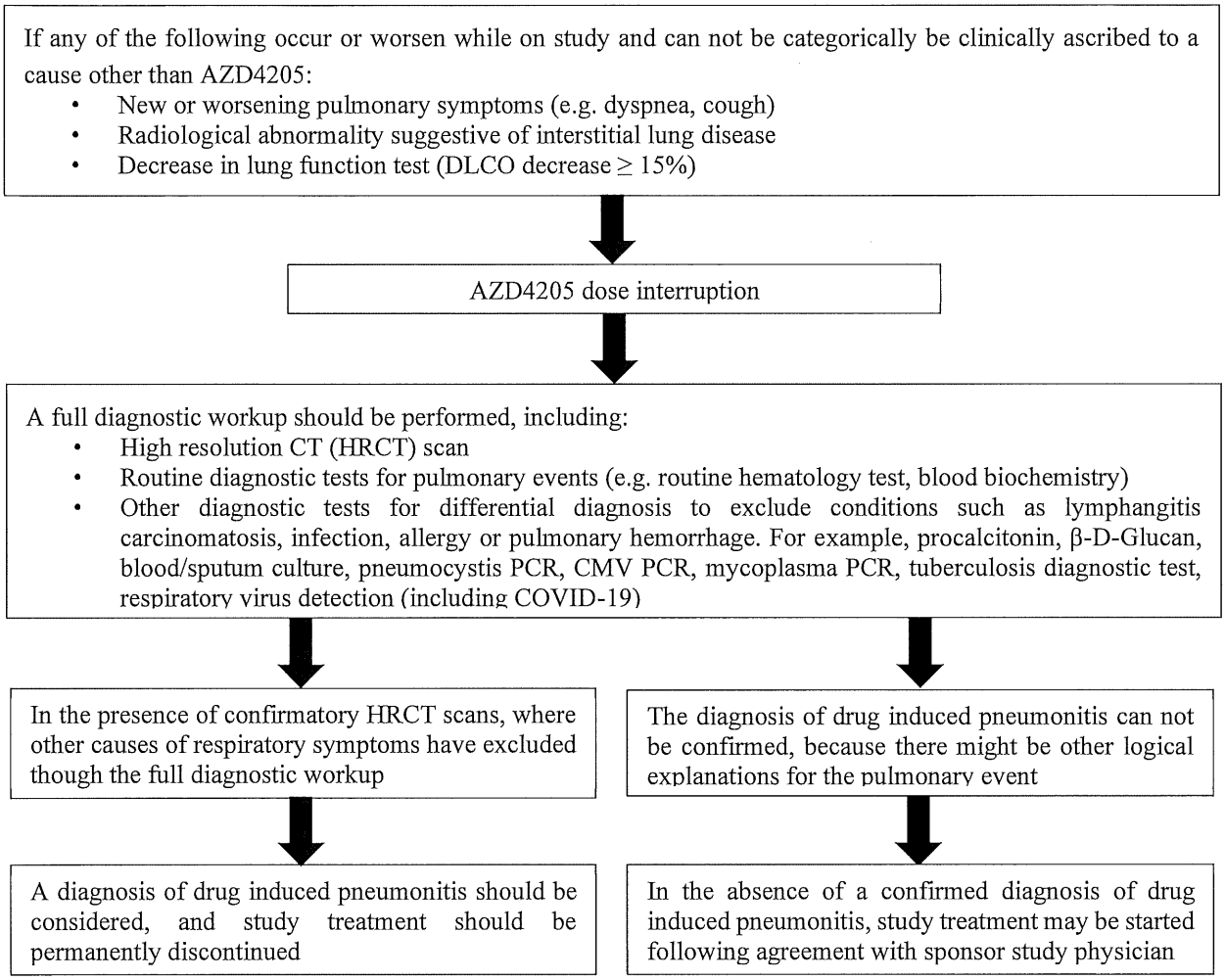
3. **Pulmonary monitoring**

- AZD4205 is a potent, oral, ATP-competitive inhibitor of JAK1 kinase. It is intended for the treatment of advanced cancer patients as monotherapy in this study.
- Preclinical studies suggest a potential association between the use of AZD4205 and the occurrence of lung events. Thus, patients with previous medical history of ILD (interstitial lung disease), drug induced ILD, radiation induced pneumonitis need steroid treatment, or any evidence of clinically active ILD, should be excluded from AZD4205 related clinical studies.
- On the other hand, serious infection including opportunistic infection such as pneumocystis carinii pneumonia (PCP) is an identified risk for many approved JAK inhibitors (e.g. tofacitinib and ruxolitinib). Given the fact that patients with lymphoproliferative disorders (e.g. lymphoma) are at a high risk for PCP infection, **prophylaxis for PCP should be taken into consideration during the study treatment.** Trimethoprim/sulfamethoxazole (TMP/SMZ) is

the preferred drug for the primary prophylaxis of PCP infections in adults. The recommended dose is a single-strength (80/400 mg) tablet daily.

- It is important that patients are fully informed that potential pulmonary events may occur during treatment with AZD4205.
- If there is any suspicion of interstitial lung disease (e.g. abnormal findings on CT scans, DLCO decrease ≥ 15%, or any related pulmonary symptoms/signs), dosing with AZD4205 should be interrupted whilst further investigations (a full diagnostic workup) are performed.
- Sometimes, the atypical pneumonia due to infection is difficult to differentiate from pneumonitis only based on radiological findings, e.g. abnormal ground glass opacity (GGO) on CT scans. Thus, **a full diagnostic workup (e.g., HRCT, pathogen detection tests, hematology tests) is highly recommended, when a pulmonary event is suspected.** The full diagnostic workup is aimed at excluding conditions such as lymphangitis carcinomatosis, infection, allergy or pulmonary hemorrhage, and the details are as below (see Figure 3):
  - High resolution CT (HRCT) scan is recommended when a pulmonary event is suspected, e.g. abnormal findings on CT scans, DLCO decrease ≥ 15%, or any related pulmonary symptoms/signs.
  - The diagnostic workup should cover routine diagnostic tests for pulmonary events (e.g. routine hematology test, blood biochemistry), and other diagnostic tests for differential diagnosis to exclude conditions such as infection, lymphangitis carcinomatosis, allergy or pulmonary hemorrhage. For example, procalcitonin, β-D-Glucan, blood/sputum culture, pneumocystis PCR, Cytomegalovirus (CMV) PCR, mycoplasma PCR, tuberculosis diagnostic test, respiratory virus detection (including COVID-19).
  - In the presence of confirmatory HRCT scans, where other causes of respiratory symptoms have excluded though the full diagnostic workup, a diagnosis of drug induced pneumonitis should be considered, and study treatment should be permanently discontinued. In the absence of a diagnosis of pneumonitis, study treatment may be started.
- Please complete the eCRF and inform sponsor as soon as a potential pulmonary event is identified. The study team will send a pneumonitis questionnaire, in order to collect more information about the event for full review and reporting.

Figure 3 ILD/Pneumonitis Assessments Flow Chart



4. Infection

Serious infections are identified risk of many approved JAK inhibitors (e.g. ruxolitinib, tofacitinib and baricitinib). On the other hand, previous heavily treated PTCL patient are also at a high risk for infections, especially opportunistic infections. So far, infections including pneumocystis pneumonia, herpes zoster and cytomegaloviral reactivations were reported in clinical studies with AZD4205.

Patients with active infection should be excluded from participating in this study, e.g. infections requiring oral or intravenous antimicrobial therapy. Subjects will be monitored for development of any infection (viral, bacterial, and fungal).

Prophylaxis for pneumocystis pneumonia

Pneumocystis carinii infection causes life-threatening pneumonia (PCP; also known as PJP) in patients with immunosuppression due to underlying malignancy, organ transplantation or other

conditions. It's known that heavily treated patients with hematological malignancies are at a high risk of PCP infection, and many approved JAK inhibitors also observed PCP infection. Hence, adequate prophylaxis is critical in high-risk conditions (Cordonnier C et al. 2016). Most cases of PCP occur from reactivation of latent infection, although cases of person-to-person transmission have been reported. In a Cochrane meta-analysis (including 1155 adult patients with acute leukemia and recipients of an HSCT and solid organ transplant), the incidence of PCP was reduced by 91% [relative risk (RR) 0.09] with prophylaxis compared with placebo, no treatment or treatment with antimicrobial agents showing no activity against P. jirovecii (e.g. quinolones) (Green H et al. 2007). Pneumocystis pneumonia has been reported in the clinical study with AZD4205. Therefore, for all patients during the treatment, pneumocystis prophylaxis is required. Please follow institutional guidelines or refer to below guidance (Maertens J et al. 2016, L. Cooley et al. 2014).

Trimethoprim/sulfamethoxazole (TMP/SMZ) is the preferred drug for the primary prophylaxis of Pneumocystis infections in adults. The recommended dose is either a single-strength (80/400 mg) tablet daily or a double-strength tablet (160/800 mg) three times weekly. Limitations in TMP/SMX prophylaxis include documented hypersensitivity, renal impairment, myelosuppression and gastrointestinal disturbance. The true rate of adverse reactions is unknown, but in the adult HSCT population it is estimated to be in the range of 5–15%, and in children it is much lower (Souza JP et al.1999).

Second-line agents for PJP chemoprophylaxis may be given to the patients if TMP/SMZ is intolerant or contraindicated, including dapsone, atovaquone or pentamidine (see Table 17).

Table 17 Dosing schedule for PCP chemoprophylaxis for adult patients with hematological malignancies

	Dosing schedule
TMP-SMZ	80 + 400 mg (one SS tablet) orally, daily Or 160 + 800 mg (one DS tablet) orally, three times a week
Dapsone	100 mg orally, daily
Pentamidine	300 mg inhaled through nebuliser, every 4 weeks (administered through a jet-nebuliser producing a droplet size of 1–2 microns)
Atovaquone	1500 mg orally, daily with a high-fat meal

Monitoring and management of cytomegaloviral infections

A few cases of cytomegaloviral (CMV) infection, including CMV chorioretinitis and/or retinal disorders related to CMV infection, were reported in the clinical trials of AZD4205. For patients with history of CMV infection that required treatment, prophylactic treatment and monitoring for reactivation via serology or viral load detection per institutional guidelines is recommended.

Besides, based on the nature and severity of CMV chorioretinitis, patients should be educated to report any changes in vision or ocular symptoms directly to their ophthalmologist.

Specially, ophthalmic examinations should be performed for all patients at baseline, Cycle 3 and then every 3 cycles (approximately every 2 months) after enrolment. The recommended ophthalmic examinations include visual acuity (corrected), intraocular pressure, slit lamp examination, and dilated ophthalmoscopy. If intraocular infection of CMV is suspected, a biopsy of intraocular fluid (aqueous humor and/or vitreous humor, depending on the involvement of the disease) is recommended to confirm the pathogen.

The following ocular adverse events should be graded according to Table 18, and if the causality is considered to be related with the study intervention, the dose should be also modified accordingly.

Table 18 Addendum to Grading of Ocular Adverse Event and Dose Modifications of Ocular Adverse Reactions

Adverse Event/Reaction	Description	Grade	Actions in Dose Modification
Keratitis	Clear cornea, no epithelial defects	Grade 0	Dosing not interrupted
	Nonconfluent superficial keratitis; asymptomatic; clinical or diagnostic observation only; intervention not indicated	Grade 1	Dosing not interrupted
	Confluent superficial keratitis; symptomatic; a cornea epithelial defect, or 3-line or less decreased vision in best corrected distance visual acuity (BCVA) from baseline	Grade 2	Drug interruption until resolved to nonconfluent superficial keratitis, then resume dose
	Corneal ulcer or stromal opacity; marked BCVA decrease, worse than 20/40 or more than 3 lines of decreased vision from baseline, up to 20/200; limiting self care activities of daily living	Grade 3	Drug interruption until resolved, then reduce dose to 75 mg
	Corneal perforation; or BCVA of 20/200 or worse in the affected eye	Grade 4	Discontinue participant from study treatment
Conjunctivitis	No vasodilation, no epithelial defects	Grade 0	Dosing not interrupted
	Nonconfluent superficial punctate defects, mild vasodilation	Grade 1	Dosing not interrupted
	Confluent superficial punctate staining, moderate to severe vasodilation.	Grade 2	Drug interruption until resolved to nonconfluent superficial keratitis, then resume dose
	Conjunctival ulcer or neovascularization.	Grade 3	Drug interruption until resolved, then reduce dose to 75 mg
	BCVA of 20/200 or worse in the affected eye	Grade 4	Discontinue participant from study treatment
Iritis/Uveitis	Clear anterior chamber	Grade 0	Dosing not interrupted

Adverse Event/Reaction	Description	Grade	Actions in Dose Modification
	Trace cell in anterior chamber	Grade 1	Dosing not interrupted
	1-2+ cell or flare in anterior chamber	Grade 2	Drug interruption until resolved to Grade 0 or 1 and then resume dose
	3+ cell or flare in anterior chamber; intermediate posterior or pan-uveitis	Grade 3	Drug interruption until resolved to Grade 0 or 1, then reduce dose to 75 mg
	Hypopyon; or BCVA of 20/200 or worse in the affected eye	Grade 4	Discontinue participant from study treatment
Serous detachment of retinal pigment epithelium	No detachment	Grade 0	Dosing not interrupted
	Detachment which starts to resolve at or within 2 weeks	Grade 1	Dosing not interrupted
	Detachment which does not start to resolve at or within 2 weeks	Grade 2	Delay dose until detachment starts to resolve, then maintain dose.
	Detachment which does not start to resolve within 2 months	Grade 3	Drug interruption until detachment starts to resolve, then reduce dose to 75 mg
Blurred vision	BCVA same as baseline BCVA	Grade 0	Dosing not interrupted
	Intervention not indicated	Grade 1	Dosing not interrupted
	BCVA worse than baseline but no worse than 20/40 and better; or 3 lines or less decreased vision from known baseline; limiting instrumental activities of daily living	Grade 2	Dosing not interrupted
	BCVA worse than baseline but no worse than 20/200; or more than 3 lines of decreased vision from known baseline; limiting self care activities of daily living	Grade 3	Drug interruption until resolved as baseline or 20/40 whichever is worse, then resume dose
	BCVA 20/200 or worse	Grade 4	Drug interruption until resolved as baseline or 20/40 whichever is worse, then reduce to 75 mg
Cytomegaloviral chorioretinitis	No evidence of retinal involvement	Grade 0	Dosing not interrupted
	No evidence of retinal involvement	Grade 1	Dosing not interrupted
	No evidence of retinal involvement	Grade 2	Dosing not interrupted
	Retinal involvement less than one disc diameter (1.5 mm)	Grade 3	Drug interruption until quiescent, then reduce to 75 mg
	Retinal involvement greater than one disc diameter	Grade 4	Discontinue participant from study treatment

Reference

Cordonnier C et al. 2016

Cordonnier C, Cesaro S, Maschmeyer G, et al. Pneumocystis jirovecii pneumonia: still a concern in patients with haematological malignancies and stem cell transplant recipients. Journal of Antimicrobial Chemotherapy, Volume 71, Issue 9, September 2016, Pages 2379–2385

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