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CANCER RESEARCH UK
Centre for Drug Development

A Cancer Research UK Phase I trial of AZD3965, a monocarboxylate transporter 1 inhibitor (MCT1) in patients with advanced cancer

Sponsor protocol number: CRUKD/12/004

EudraCT number: 2010-024463-41

Chief Investigator: Professor Elizabeth Ruth Plummer
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Sponsor: Cancer Research UK
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PARTICIPATING INVESTIGATORS AND CENTRES:

The List of Participating Investigators and centres can be found in the Trial Master File and Investigator Trial Files.

PROTOCOL VERSION HISTORY:

Version No.	Issue Date	Reason for update
1.0	29 August 2012	Initial version submitted for regulatory and ethical approval.
2.0	30 October 2012	Addition of QTc interval DLT criteria in Section 3.1.4 and maximum administered dose added to Section 5.3 at the request of the MHRA. New sections - 2.2.9 Maximum Exposure and 5.2 Maximum Exposure Limit added.
3.0	02 April 2013	Amend and clarify the type of ERG assessments performed in Section 7, clarify Exclusion criteria 17 in Section 4, include information on patient sickness in relation to drug administration, amend appendices. Correct inconsistencies and other minor errors.
4.0	11 October 2013	Removal of Week 2 and 4 ophthalmic tests. Amendment to PK and PD time points, inclusion of a new tertiary/research assay and subsequent addition of a new tertiary objective. Reduction in the time frame between the first and second patient in each cohort.
5.0	27 March 2014	Introduction of rolling six design to Part 1 dose escalation phase allowing up to six evaluable patients to be treated at each dose level. CDD Medical Advisor may accept blood tests performed before Day -14 to confirm eligibility if not clinically relevant to repeat. Ongoing toxic manifestations of previous treatments of Grade 1 are acceptable; Grade 2 toxicities should be discussed with CDD Medical Advisor to evaluate eligibility.
6.0	29 March 2015	[redacted] Further guidance on management of troponin rise. Allow patients to participate in interventional trials which do not involve an IMP. Removal of the need for one female in each cohort in Part 1. Change in department name of the sponsor to Centre for Drug Development.
7.0	03 March 2016	[redacted] Amendment to the window allowance of Salvia pH samples taken on Day -7 as well as Ophthalmic tests performed during continuous dosing of AZD3965 treatment.
8.0	07 February 2017	Update to Part 2 of the study; including patient population, eligibility criteria, objectives and endpoints, investigations, schedule of events and sampling.
9.0	24 August 2017	Update to eligibility criteria; additional lactate and bicarbonate screening sample required as well as clarification to the Part 2 sampling assays.
10.0	18 December 2017	Clarification to Day -7 dose as this refers to the total dose administered on that day. This can be either once daily dosing or twice daily dosing.

Version No.	Issue Date	Reason for update
		Update to the Part 1 and Part 2 Sampling Summaries to bring in line with the current protocol template.
11.0 **(not implemented)**	29 May 2018	Update to eligibility criteria: • Additional guidance added to exclusion criteria #1 related to wash out periods for previous therapies. • Additional guidance added to exclusion criteria #19 to include patients with low risk prostate cancer who are on surveillance. • Fasting glucose has been updated from <6.1 mmol/L in the inclusion criteria for Part 2 of the study to <7.8 mmol/L. • Patients with Type 1 diabetes controlled on insulin (but not oral anti-diabetic medication) can now be included in the study. • IHC will be performed retrospectively once the patient has enrolled on the study rather than at pre-screening to confirm the patients' MCT1 and MCT4 expression. Expression is no longer part of the eligibility criteria. • Update to exclusion criteria #15 to add further clarification and to allow patients with a first degree heart block to be included in the study. • Update to exclusion criteria #16 to allow patients who have had a prior allogeneic bone marrow transplant. Removal of Day -7 dosing during Part 2 of the study and rearrangement of some on-study assessments to accommodate this. Lactate and bicarbonate testing added to Cycle 1 Day 1. Ophthalmology assessments removed from Part 2 of the study apart from best corrected visual acuity and ERG tests. [redacted] Section 7 now only includes the schedule for Part 1 of the study. Section 8 has been incorporated into the protocol and contains the schedule for Part 2 of the study only. Update of number of patients entering Part 2 of the study from '15 – 20 patients' to 'up to 20 patients'. Further guidance added on concomitant medication and treatment, including current list of drugs known to cause QT prolongation. Clarification of investigations to be performed on fresh (new) on study paired tumour biopsy samples.
12.0	22 August 2018	CTA amendment 13 (incorporating Protocol version 11.0) was rejected by the MHRA on 03 July 2018. CTA amendment 14 (incorporating Protocol version 12.0) addresses the GNA points raised by the MHRA for CTA amendment 13. Protocol version 12.0 incorporates changes from Protocol version 11.0 plus:

Version No.	Issue Date	Reason for update
		• Update to exclusion criteria #3 from 'known' to 'symptomatic brain or leptomeningeal tests' now classed as a substantial amendment. • Mandatory ECG to be performed 24 hours after first dose of AZD3965.
13.0	27 March 2019	• [redacted] • Wording in inclusion criterion number 1, pertaining to Part 2 of the study has been updated from 'relapsed or refractory to conventional treatment' to 'relapsed or refractory or both to conventional treatment.' • Definitions of DLBCL (diffuse large B cell Lymphoma) or BL (Burkitt's Lymphoma) relapsed and refractory added to inclusion criterion number 1, pertaining to Part 2 of the study. • Update to exclusion criterion number 9; [redacted] • Update to exclusion criterion number 14; patients with Diabetes Mellitus Type 1 and Type 2 can be included on the study if they are diet controlled or insulin controlled with a fasting glucose <7.8 mmol/l and normal HbA1c. • Use of potential prohibited concomitant medications can now be discussed on a patient by patient basis with the CDD and CI in Part 2 of the study. • Additional guidance regarding the use of prohibited concomitant medications during a break in AZD3965 dosing. A patient can re-start AZD3965 only when 5 half lives of the prohibited concomitant medication has been reached. • [redacted] • Addition of wording regarding SAEs to be reported when a patient is in pre-screening (SAEs only to be reported if related to study assessments i.e. biopsy). • In Sections 7 and 9 of the protocol, the schedule of events and sampling for Part 1 of the study has been removed. See Protocol version 12.0 for Part 1 details.
14.0	04 February 2020	• [redacted] • Inclusion of requirement for continued patient benefit and physician review from Cycle 13 onwards. • Annex 13 label has been updated to include PI name and site address, therefore Section 6.1 updated to reflect this change. • Evaluations from Cycle 13 onwards added to Section 8.5. • Section 8.8.1 Schedule of events for Part 2, Cycle 13 onwards added.

Version No.	Issue Date	Reason for update
		• [redacted] • CSR data cut off added to Section 14 and 15.5. • Updated throughout to remove limit of 12 cycles. • Blood volumes updated throughout to reflect Cycle 13 onwards. • [redacted] • General typographical and formatting updates throughout.

TABLE OF CONTENTS

TITLE PAGE
TABLE OF CONTENTS
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS
PROTOCOL SIGNATURES

1 PROTOCOL SUMMARY 15

1.1 Full title 15
1.1.1 Short title 15
1.2 Clinical trial objectives and endpoints 15
1.2.1 Primary objectives and endpoints 15
1.2.2 Secondary objectives and endpoints 15
1.2.3 Tertiary objectives and endpoints 16
1.3 Design 16
1.4 Administration schedule 16
1.5 Treatment group 17
1.6 Trial timelines 17

2 INTRODUCTION 18

2.1 Background 18
2.1.1 Monocarboxylate transporter 1 (MCT1) and Cancer 18
2.2 Investigational medicinal product 19
2.2.1 Structure of AZD3965 19
2.2.2 Mechanism of action of AZD3965 19
2.2.3 Non-clinical pharmacology 19
2.2.4 Safety pharmacology 20
2.2.5 Pharmacokinetics and metabolism 21
2.2.6 Toxicology 22
2.2.7 Starting dose for Phase I and dose escalation considerations 25
2.2.8 Starting dose 25
2.2.9 Maximum Exposure 26
2.3 Clinical experience 26
2.4 Rationale for the proposed trial 26

3 TRIAL DESIGN 27

3.1 Clinical trial objectives and endpoints 27
3.1.1 Primary objectives and endpoints 27
3.1.2 Secondary objectives and endpoints 27
3.1.3 Tertiary objectives and endpoints 28
3.1.4 Definition of dose limiting toxicity 28
3.1.5 Definition of maximum tolerated dose 30
3.2 Patient evaluability 30
3.3 Design of the clinical trial 30

4 PATIENT SELECTION 32

4.1 Eligibility criteria 32
4.1.1 Inclusion criteria: 32
4.1.2 Exclusion criteria: 34
4.2 Patient enrolment 35

5 TREATMENT 35

5.1 Selection of the Phase I starting dose and schedule (Part 1) 35
5.2 Maximum Exposure Limit 35
5.3 Dosing schedule/treatment schedule (Parts 1 and 2) 36
5.4 Dose escalation scheme (Part 1) 36

5.4.1 Intra-patient dose escalations ... 37
5.4.2 Expansion of dose level(s) ... 37
5.5 Dose modifications ... 37
5.5.1 Dose withdrawal ... 37
5.5.2 Dose reductions ... 38
5.5.3 Dose delays ... 38
5.6 Missed Doses ... 38
5.7 Duration of treatment ... 38
5.7.1 Replacement of patients ... 39
5.8 Concomitant medication and treatment ... 39

6 PHARMACEUTICAL INFORMATION ... 40

6.1 Supply of AZD3965 ... 40
6.2 Pharmaceutical data ... 40
6.2.1 Formulation of AZD3965 ... 40
6.2.2 Storage conditions ... 41
6.2.3 Stability of AZD3965 ... 41
6.2.4 Dispensing of AZD3965 ... 41
6.2.5 AZD3965 administration ... 41
6.3 AZD3965 accountability ... 42

7 INVESTIGATIONS SCHEDULE FOR PART 1 OF THE STUDY ... 43

8 INVESTIGATIONS SCHEDULE FOR PART 2 OF THE STUDY ... 44

8.1 Pre-treatment evaluations ... 44
8.1.1 Obtaining written informed consent ... 44
8.1.2 Pre-screening ... 45
8.1.3 Evaluations within four weeks prior to first dose (Day -28 to Day -1) ... 45
8.1.4 Evaluations within two weeks prior to first dose (Day -14 to Day -1) ... 45
8.1.5 Evaluations within one week prior to first dose (Day -7 to Day -1) ... 46
8.2 Evaluations on Cycle 1 Day 1 (+/- 24 hours) ... 46
8.3 Evaluations at 24 hours (± 2 hours) after the first dose of AZD3965 treatment ... 47
8.4 Evaluations during continuous AZD3965 treatment Cycles 1–12 (excluding Cycle 1 Day 1) ... 47
8.5 Evaluations from Cycle 13 onwards ... 48
8.6 Evaluations at 'Off-Study' visit ... 50
8.7 Follow-up ... 50
8.8 Schedule of events for Part 2 (Cycles 1-12) of the study ... 51
8.8.1 Schedule of events for Part 2, Cycle 13 onwards ... 53

9 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS ... 54

9.1 Part 1 Sampling summary ... 54
9.2 Part 2 Sampling summary ... 55
9.3 Primary assay – Pharmacodynamic - Lactate accumulation in PBMCs (Part 1 only) ... 57
9.4 Secondary assays ... 57
9.4.1 Secondary Assays - AZD3965 Pharmacokinetics ... 57
9.4.2 Secondary assays – Pharmacodynamics - Cell Death Biomarkers (M65, M30, nDNA) (Part 1 only) ... 57
9.5 Tertiary/research assays ... 57
[redacted]
9.6 Storage and Shipment of Samples ... 61

10 ASSESSMENT OF SAFETY ... 61

10.1 Investigator responsibilities ... 61
10.1.1 Medical cover ... 61

10.2 Adverse event definitions 61
10.2.1 Adverse event 61
10.2.2 Serious adverse events 61
10.2.3 Suspected, unexpected, serious adverse reactions 62
10.2.4 Determining adverse event causality 62
10.2.5 Expectedness 63
10.3 Collecting of safety information 63
10.3.1 Pre-Screening 63
10.3.2 Screening failures 64
10.3.3 Eligible patients 64
10.3.4 Follow-up of AEs and SAEs 64
10.3.5 Other safety information of interest 64
10.4 Reporting of SAEs to the Pharmacovigilance Department, CDD 64
10.4.1 Events exempt from being reported as SAEs to the Pharmacovigilance department 65
10.5 Recording of adverse events and serious adverse events in eCRFs 65
10.6 Urgent safety measures 65
10.7 Pregnancy 65

11 ASSESSMENT OF EFFICACY 66

11.1 Measurement of disease 66
11.2 Timing and type of tumour assessments 66
11.2.1 Baseline evaluations 67
11.2.2 Evaluations during and at Off-study visit 67
11.3 Tumour response 67
11.3.1 Recording of response in the eCRF 68
11.3.2 Other definitions of outcome 68

12 PATIENT WITHDRAWAL BEFORE COMPLETION OF TREATMENT SCHEDULE 68

13 DEFINING THE END OF TRIAL 68

14 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS 69

14.1 Presentation of data 69
14.2 Safety 69
14.3 Pharmacokinetics 70
14.4 Pharmacodynamics – lactate accumulation in PBMCs (Part 1 only) 70
14.5 Anti-tumour activity 70
14.6 Exploratory work 70

15 ADMINISTRATION 70

15.1 Protocol deviations and amendments 70
15.2 Completion of the electronic case report form (eCRF) 70
15.3 Trial performance and monitoring 71
15.4 Source document verification 71
15.5 Clinical study report (CSR) 72
15.6 Record retention 72
15.7 Ethical considerations 72
15.8 Indemnity 72
15.9 Publication policy and press releases 72

16 REFERENCES 74

17 APPENDICES 75

17.1 APPENDIX 1: WHO PERFORMANCE SCALE 75
17.2 APPENDIX 2A: MEASUREMENT OF DISEASE IN SOLID TUMOURS 76
17.3 APPENDIX 2B: MEASUREMENT OF DISEASE IN LYMPHOMA 86
17.4 APPENDIX 3: CONCURRENT MEDICATION WITH A KNOWN RISK OF QT PROLONGATION 89
17.5 APPENDIX 4: MANAGEMENT OF EYE TOXICITY 99

17.6 APPENDIX 5: Severe valvular heart disease (as defined by British Society of Echocardiography) 100

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
A	ABPI	Association of the British Pharmaceutical Industry
	AE	adverse event
	ALP	alkaline phosphatase
	ALT	alanine aminotransferase
	ANC	absolute neutrophil count
	AST	aspartate aminotransferase
	ATP	adenosine tri-phosphate
	AUC	area under the curve
	AZ	Astra Zeneca
B	Bid	"bis in die"- twice a day
	BL	Burkitt Lymphoma
	BP	blood pressure
C	^{0}C	degrees Celsius
	CDD	Centre for Drug Development
	CI	Chief Investigator (formerly Co-ordinating Investigator)
	C_{max}	maximum observed plasma concentration
	CR	complete response
	CRA	Clinical Research Associate
	eCRF	electronic case report form
	CR-UK	Cancer Research UK
	CSM	Clinical Study Manager
	CT	computerised tomography
	CTA	clinical trial authorisation
	CTC	circulating tumour cell
	CTCAE	Common Terminology Criteria for Adverse Events
	ctDNA	circulating tumour deoxyribonucleic acid (DNA)
	CXR	chest x-ray
D	Day	calendar day
	DBP	diastolic blood pressure
	DLBCL	diffuse large B cell lymphoma
	DLT	dose limiting toxicity
E	ECG	electrocardiogram
	ECHO	echocardiogram
	EDC	electronic data capture
	EDTA	ethylene diamine tetra-acetic acid
	EF	ejection fraction
	EP	early progression
	ERG	electroretinogram
F	FDG	fluorodeoxyglucose
	ffERG	full field electroretinogram
G	GCP	Good Clinical Practice
	g/dL	gram(s) per decilitre
	GMP	Good Manufacturing Practice
H	Hb	haemoglobin
	HBF	hepatic blood flow
	hERG	Human Ether-a-go-go Related Gene
	HCG	human chorionic gonadotropin
	HIV	human immunodeficiency virus
	HNSTD	highest non seriously toxic dose
	HR	heart rate
	HRA	Health Research Authority

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
I	IB	Investigator's Brochure
	ICH GCP	International Conference on Harmonisation of Good Clinical Practice
	IHC	Immunohistochemistry
	IMP	investigational medicinal product
	ITF	Investigator Trial File
	IUD	Intra-uterine device
	IWG	international working group
K	kg	kilograms
L	LDH	lactate dehydrogenase
	L-HPC	low-substituted hydroxylpropyl-cellulose
	LVEF	left ventricular ejection fraction
M	MAD	maximum administered dose
	MCT	monocarboxylate transporter
	MDR	multi-drug resistance
	min	minutes
	mg/m^2	milligram per square metre
	mg	milligrams
	mL	milliliters
	MHRA	Medicines and Healthcare products Regulatory Agency
	MRI	magnetic resonance imaging
	MRS	magnetic resonance spectroscopy
	msec	millisecond
	MTD	maximum tolerated dose
N	NCI	National Cancer Institute
	NE	not evaluable
	NHL	non-Hodgkin's Lymphoma
	NOAEL	no observed adverse effect level
	NOEL	no observed effect level
	nM	nanomolar
	NYHA	New York Heart Association
O	OCT	optical coherence tomography
P	PBMC	peripheral blood monocytes
	PD	pharmacodynamic OR progressive disease
	pERG	pattern electroretinogram
	PET	positron emission tomography
	PI	Principal Investigator
	PK	pharmacokinetic
	PR	partial response
	PSA	prostate specific antigen
	PSRB	Protocol and Safety Review Board
	PT	prothrombin time
	PXR	pregnane X receptor
Q	qd	quaque die – once a day
	QP	Qualified Person
	QTcF	Fridericia's correction: $QTc = QT/RR^{0.33}$
R	REC	Research Ethics Committee
	RECIST	Response Evaluation Criteria in Solid Tumours
	RP2D	recommended phase II dose
S	SAE	serious adverse event
	SBP	systolic blood pressure
	SD	stable disease

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
	SDV	source data verification
	SOP	standard operating procedure
	SUSAR	suspected unexpected serious adverse (drug) reaction
T	$T_{1/2}$	terminal elimination half-life
	T_{max}	time to reach C_{max}
	TdP	Torsades De Pointes
U	ULN	upper limit of normal
	USM	urgent safety measure
W	WBC	white blood cell
	WHO	World Health Organisation

PROTOCOL SIGNATURES

Sponsor Signature

The Sponsor has read and agrees to the protocol, as detailed in this document. I am aware of my responsibilities as the Sponsor under the UK Clinical Trials Regulations[1], the guidelines of Good Clinical Practice (GCP)[2], the Declaration of Helsinki[3], the applicable regulations of UK law and the trial protocol. The Sponsor agrees to conduct the trial according to these regulations and guidelines and to appropriately direct and assist sponsor's staff who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Name: _____

Title _____

Signature: _____

Date: _____

[1] *The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.*

[2] *ICH Harmonised Guideline Integrated Addendum to ICH E6: Guideline for Good Clinical Practice E6(R2) Step 4 dated 09 November 2016).*

[3] *WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and all subsequent amendments including Oct 2013.*

PROTOCOL SIGNATURES

Investigator's Signature

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the UK Clinical Trials Regulations[1], the guidelines of Good Clinical Practice (GCP)[2], the Declaration of Helsinki[3], the applicable regulations of the relevant NHS Trusts and the trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Investigator's Name: _____

Name of site: _____

Signature: _____

Date: _____

1 PROTOCOL SUMMARY

1.1 Full title

A Cancer Research UK Phase I trial of AZD3965, a monocarboxylate transporter 1 inhibitor (MCT1) in patients with advanced cancer.

1.1.1 Short title

A Phase I trial of AZD3965 in patients with advanced cancer.

1.2 Clinical trial objectives and endpoints

1.2.1 Primary objectives and endpoints

Primary Objectives	Endpoints
1. To propose a recommended Phase II dose (RP2D) of AZD3965 and/or the maximum tolerated dose (MTD) in patients with advanced cancer, given via oral administration	1. Determining a dose at which no more than one patient out of up to six patients at the same dose level experiences a highly probable or probably drug-related dose limiting toxicity (DLT) and/or a biological effective dose based on pharmacokinetic (PK) and pharmacodynamic (PD) endpoints.
2. Establishing the safety profile of AZD3965	2. Determining causality of each adverse event to AZD3965 and grading severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.02.

1.2.2 Secondary objectives and endpoints

Secondary Objectives	Endpoints
1. To investigate the pharmacokinetic (PK) behaviour of AZD3965 in patients with advanced cancer	1. Determining the plasma levels of AZD3965 after single and multiple doses of AZD3965.
2. Part 2: To assess the potential anti-tumour activity of AZD3965 in patients with relapsed or refractory diffuse large B cell Lymphoma (DLBCL) and/or Burkitt Lymphoma (BL)	2. Objective response: stable disease (SD), partial response (PR), or complete response (CR) according to Response Criteria Evaluation (RECIST, version 1.1) or International Working Group criteria for Lymphoma (see appendix 2A and 2B).

1.2.3 Tertiary objectives and endpoints

1.3 Design

This is a multi-centre, dose escalation, Phase I trial in two parts.

In Part 1 each patient cohort included up to six evaluable patients following a rolling six dose escalation scheme (Skolnik A.M. *et al*., 2008) of AZD3965 until a recommended Phase II dose (RP2D) and/or the maximum tolerated dose (MTD) was defined.

42 patients with advanced solid tumours or Lymphoma were entered into Part 1. The final number depended on the number of dose escalations required to reach MTD or the tolerated dose at which monocarboxylate transporter 1 (MCT1) was inhibited. A RP2D was proposed from the safety and pharmacokinetic (PK) results from Part 1.

All patients in Part 2 will be treated at this RP2D to further explore the tolerability of this dose and schedule and to explore proof of principle of MCT1 inhibition in tumour types that were shown to express high MCT1 and low monocarboxylate transporter 4 (MCT4) or in which AZD3965 showed some effect pre-clinically.

In Part 2 there will be up to 20 evaluable patients entered with relapsed or refractory diffuse large B cell Lymphoma (DLBCL) and Burkitt Lymphoma (BL).

1.4 Administration schedule

AZD3965 is available as 5, 10, 20 and 30 mg capsules and patients will take their dose orally once or twice every day (in the absence of toxicity).

One treatment cycle will consist of 28 days (with Cycle 1 including an additional dosing day at Day -7[4] for Part 1 of the trial only).

In the Part 1 dose escalation, up to six evaluable patients were treated at each dose level with a dose on Day -7 followed by continuous daily dosing starting on Day 1 (in the absence of toxicity after the Day -7 dosing).

The starting dose was 5 mg once daily and the next total daily dose level was 10 mg.

Pharmacokinetic (PK) assessments were performed to assess the half-life and potential accumulation of the drug in order to inform whether dosing for future cohorts should be once or twice daily.

The total daily dose was doubled in successive cohorts until a Grade 2 highly probable or probably related adverse drug reaction was reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.02. Subsequent dose increases between cohorts were up to a maximum of 50% (to the nearest 5 mg) driven by reported safety, PK and pharmacodynamic (PD) data. However, an upper limit on dose escalation was set using PK data (see Section 2.2.9). If continuous daily dosing is not tolerated at levels that inhibit MCT1 then intermittent schedules will be explored.

Up to six evaluable patients were treated at each dose level. At least one male patient was treated in each cohort [redacted] If a dose limiting toxicity (DLT) was observed then the cohort was expanded to six patients. If a second DLT was reported no further dose escalation was performed and a total daily dose level below was expanded to six patients to identify the MTD.

An interval of 14 days (from Day -7 (7 days prior to Day 1) was observed between the recruitment of the first and second patients in a cohort but the subsequent patients were treated in parallel. Twenty-eight days (from Day 1) of data (safety, PK and PD) was available for a minimum of three patients in a cohort in order to make the decision to dose escalate.

In both Parts 1 and 2, AZD3965 will be administered as continuous daily dosing in 28 day cycles for up to six cycles. If the patient is benefitting from the treatment, a further six cycles may be administered after discussions between the Investigator and the Sponsor, Cancer Research UK's Centre for Drug Development (CRUK CDD). In the case of toxicity, treatment will be interrupted and then resumed when all toxicities have returned to Grade 1 or baseline. Intermittent dosing schedules may be explored based on observed toxicities.

In Part 2 all patients will be treated at the RP2D determined in Part 1. There will be no Day -7 dose in Part 2. All patients in Part 2 will be treated at the RP2D as continuous daily dosing in 28 day cycles for up to six cycles starting on Day 1. If the patient has not progressed after six cycles, further cycles may be given after discussion between the Investigator and the CDD (see Section 5.7).

An interval of 14 days (from Cycle 1 Day 1) must be observed between the recruitment of the first and second patient in the expansion cohort but subsequent patients can be treated in parallel. Data must be available (safety and PK) for a minimum of three evaluable patients in order to make any decision to change the Part 2 dose (RP2D). Any changes to the Part 2 dose (RP2D) will be for safety reasons and to decrease the total daily dose only.

1.5 Treatment group

42 patients with advanced solid tumours were entered into Part 1, and up to 20 evaluable patients with DLBCL and BL will be entered into Part 2. The final total patient numbers will depend on the number of dose levels explored in Part 1 and the number of patients recruited to Part 2.

1.6 Trial timelines

It was expected that the trial would have a minimum duration of 36 months in Part 1 and will have a minimum duration of 24 months in Part 2.

[4] Day -7 dosing may be performed on Day -8 to Day -6. See Section **Error! Reference source not found.**

2 INTRODUCTION

2.1 Background

2.1.1 Monocarboxylate transporter 1 (MCT1) and Cancer

AZD3965 is a first in class, potent and selective MCT1 inhibitor originally developed by AstraZeneca (AZ). AZD3965 targets the increased dependency on the glycolytic pathway for adenosine tri-phosphate (ATP) generation present in many tumour types, by preventing the excess lactic acid from being exported via MCT1 thereby resulting in acidosis and cell death. As such AZD3965 represents a novel potential mechanism of action to target tumour cells and an opportunity of bringing a new class of agents into the clinic.

The tumour cell population is heterogeneous as tumours contain both oxygenated and hypoxic regions (Sonveaux et al., 2008). Normal differentiated cells rely primarily on mitochondrial oxidative phosphorylation to generate the energy needed for cellular processes. In contrast most tumour cells have an increased dependency on the glycolytic pathway for ATP generation either via aerobic glycolysis (Warburg effect) or anaerobic glycolysis (Pasteur effect) as a consequence of tumour hypoxia. This glycolytic phenotype offers a number of survival advantages to the tumour as it allows the cell to meet its energetic and anabolic requirements, survive in fluctuating oxygen tensions and to generate glycolytic intermediates that can be used to fuel additional biosynthetic pathways. Key tumour associated pathways drive this phenotype including Myc, p53, Ras and hypoxia leading to the upregulation of a number of glycolytic enzymes and glucose/lactate transporters in tumours.

Therefore, as a result of the preferential utilisation of the glycolytic pathway and lactate production by tumour cells, the primary hypothesis is that inhibiting MCTs will prevent lactate transport out of cells, thereby generating both feedback inhibition of glycolysis and a pH imbalance that can lead to cytostatic or cytotoxic effects.

A secondary hypothesis, that is less well developed but supported by the expression profile of enzymes and transporters in tumour tissues, proposes that normoxic tumour-associated stromal cells, or normoxic tumour cells, can take up lactate via MCTs and use this as an energy source by converting it back to pyruvate. In this model, inhibition of lactate uptake would increase the glucose dependency of the normoxic cells and therefore deprive hypoxic or Warburg tumour cells of glucose (Sonveaux et al., 2008). Monocarboxylate transporter 1 inhibition is thus a potential anti-tumour strategy that would indirectly eradicate hypoxic/glycolytic tumour cells.

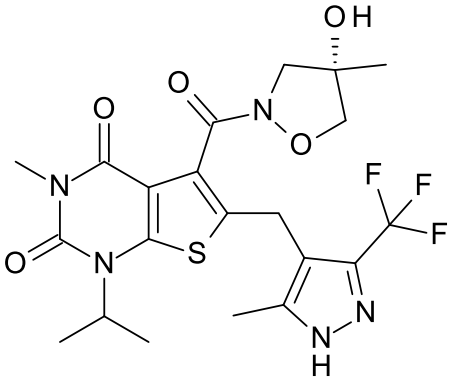
[redacted]

In many tissues, more than one MCT isoform is found which would appear to correlate with either the influx or efflux of lactic acid into different cell types. For example in skeletal muscle, the white fibres are glycolytic and contain primarily MCT4, the lactic acid effluxed by this transporter is then taken up and oxidised by the red fibres that express primarily MCT1. Similarly glial cells in the brain, which contains both MCT1 and MCT4, can export lactic acid to be oxidised by the neurons that contain MCT1 and MCT2. As AZD3965 is a selective and potent MCT1 inhibitor global MCT inhibition across all isoforms should not occur. It is therefore hypothesised that in normal cells, when MCT1 is inhibited, the presence of other MCTs will transport lactate out of the cells to maintain the body's normal homeostasis. Accordingly the presence of MCT4 has been validated as a resistance mechanism in tumour cells since introduction of MCT4 into a cell line expressing only MCT1 prevents both lactate accumulation and the inhibition of cell growth by MCT1 inhibitors. This is supported by cell panel data which shows that tumour cell lines that predominantly express MCT1 tend to be highly sensitive to AZD3965, whereas those that co-express MCT4 are far less sensitive or resistant.

2.2 Investigational medicinal product

2.2.1 Structure of AZD3965

Details of the physical and chemical characteristics of AZD3965 are provided in the investigator brochure.



2.2.2 Mechanism of action of AZD3965

The scientific rationale for the proposed trial is that many tumours have an increased dependency on the glycolytic pathway for ATP generation either via aerobic glycolysis or anaerobic glycolysis. Intracellular lactate produced by glycolysis is transported out of cells by the MCTs 1, 2, 3 and 4. Therefore by inhibiting MCT1, AZD3965 has the potential to inhibit the export of lactate from tumour cells, leading to lactate accumulation resulting in acidosis and cell death.

2.2.3 Non-clinical pharmacology

[redacted]

[redacted]

2.2.4 Safety pharmacology

[redacted]

[redacted]

2.2.5 Pharmacokinetics and metabolism

[redacted]

[redacted]

[redacted] be relevant in man and this effect may be confined to the high doses used in preclinical studies.

2.2.6 Toxicology

[redacted]

[redacted]

[redacted]

2.2.7 Starting dose for Phase I and dose escalation considerations

2.2.7.1 MTD based approach

[redacted]

2.2.7.2 Predictive pharmacology based approach

[redacted]

2.2.8 Starting dose

[redacted]

2.2.9 Maximum Exposure

Based on the nature of adverse effects observed in non-clinical studies, dose escalation to maximum tolerated dose would not be appropriate for AZD3965 in man. Dose escalation could be stopped based on pharmacodynamic (PD) effects, e.g. PBMC lactate accumulation. However, there is limited clinical experience with the planned PD assays in this study, and these assays alone are not felt to be sufficient to inform dose escalation decisions with the appropriate degree of certainty. Instead an upper limit to the dose escalation of AZD3965 has been based on exposure levels.

[redacted]

In the CRUKD/12/004 trial, patients will undergo extensive clinical monitoring for potential retinal toxicity, which is expected to be reversible should it occur. A maximum AZD3965 exposure limit in humans is therefore set as a dose of AZD3965 producing a C_{max} not in excess of 5 µM and an AUC not in excess of 20 µmol•h/L. These levels of AZD3965 should allow dose escalation into the anticipated therapeutic range while remaining below the levels likely to affect retinal function. These levels may produce some QTc effects but these are likely to be minor and short-lived post-dosing. Based on extrapolation from nonclinical data, these exposure levels might be reached with a daily dose of around 500 mg/day.

[redacted]

Assessments of exposure will be based on Day -7, Day 1 and Day 29 pharmacokinetics from Part 1. If pharmacokinetics from any of these analyses indicate that the exposure cap has been exceeded the cohort will be completed (toxicity permitting) but no further dose escalations will take place. Pharmacokinetic data from all patients in a cohort must be available prior to dose escalation. If the drug demonstrates a good safety profile at doses producing exposures close to the planned cap a substantial amendment will be requested to allow further dose escalation.

2.3 Clinical experience

This is the first time an MCT-1 inhibitor will be given to humans.

2.4 Rationale for the proposed trial

AZD3965 is a first-in class agent in clinical development and this trial will be the first time AZD3965 will be administered in humans. Many tumours have an increased dependency on the glycolytic pathway for ATP generation either via aerobic glycolysis or anaerobic glycolysis. Intracellular lactate produced by glycolysis is transported out of cells by the MCTs 1, 2, 3 and 4. Therefore by inhibiting MCT1, AZD3965 has the potential to inhibit the export of lactate from tumour cells, leading to intracellular lactate accumulation resulting in lactic acidosis and cell death.

The first part of the trial followed a rolling six dose escalation schedule. [redacted] In addition, a dose of AZD3965 was given one week before the continuous treatment started to ensure patient safety.

In Part 2, up to 20 evaluable patients with relapsed or refractory diffuse large B cell Lymphoma (DLBCL) or Burkitt Lymphoma (BL) will be treated at the recommended phase II dose (RP2D) determined in Part 1. These tumour types were chosen based on AZD3965 activity that has been demonstrated in preclinical models of DLBCL and BL and on high MCT1 expression that has been reported in DLBCL and BL samples analysed by immunohistochemistry (IHC).

[redacted]

3 TRIAL DESIGN

In Part 1 each patient cohort included a maximum of six evaluable patients following a rolling six dose escalation scheme (Skolnik A.M. et al., 2008) of AZD3965 until a RP2D and/or the MTD was defined.

A total of 42 patients with advanced solid tumours were recruited into Part 1 of the study, 40 of whom received AZD3965.

A RP2D was proposed from the safety and PK results from Part 1.

All patients in Part 2 will receive AZD3965 at this RP2D to further explore the tolerability of this dose and schedule and to explore proof of principle of MCT1 inhibition in tumour types that are known to express high levels of MCT1 and low levels or no MCT4 which showed activity in pre-clinical models.

There will be up to 20 evaluable patients with relapsed or refractory DLBCL or BL entered into Part 2.

3.1 Clinical trial objectives and endpoints

3.1.1 Primary objectives and endpoints

Primary Objectives	Endpoints
1. To propose a RP2D of AZD3965 and/or the MTD in patients with advanced cancer, given via oral administration,	1. Determining a dose at which no more than one patient out of up to six patients at the same dose level experiences a highly probable or probably drug -related DLT and/or a biological effective dose based on PK and PD endpoints.
2. Establishing the safety profile of AZD3965,	2. Determining causality of each adverse event to AZD3965 and grading severity according to the NCI CTCAE version 4.02,

3.1.2 Secondary objectives and endpoints

Secondary Objectives	Endpoints
1. To investigate the PK behaviour of AZD3965 in patients with advanced cancer,	1. Determining the plasma levels of AZD3965 after single and multiple doses of AZD3965,

2. Part 2: To assess the potential anti-tumour activity of AZD3965 in patients with relapsed or refractory DLBCL and/or BL.	2. Objective response: SD, PR, or CR according to RECIST, (version 1.1) or International Working Group criteria for Lymphoma (see Appendix 2A and 2B),

3.1.3 Tertiary objectives and endpoints

3.1.4 Definition of dose limiting toxicity

The DLT and MTD are defined using the NCI CTCAE Version 4.02.

Only DLTs identified during Part 1 Cycle 1 (including Day-7 in Part 1) informed the decision to dose escalate through the increasing dose levels. Dose limiting toxicities will be defined throughout the treatment period and will be considered in determining the RP2D for Part 2.

Any DLTs experienced during Part 2 will be collected to assist with assessment of adverse events (AEs) and patient safety profiles and the dose may be adjusted accordingly. Any changes to the Part 2 dose (RP2D) will be for safety reasons and to decrease the total daily dose only.

A DLT is defined as highly probably or probably **drug related**:

Haematological:

- neutropenia Grade 4 for ≥5 days duration
- febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) with Grade 3 or 4 neutropenia (absolute neutrophil count - ANC $<1.0x10^9$/L and fever ≥38.5°C)
- infection (documented clinically or microbiologically) with Grade 3 or 4 neutropenia (ANC $<1.0x10^9$/L)

- thrombocytopenia Grade 4: a) for ≥5 days*, or b) associated with active bleeding, or c) requiring platelet transfusion.

Cardiac:

- QTc interval >500 msec or an increase of >60 msec from baseline (verified manually (Fridericia's correction (QTcF))
- Any other Grade 3 or 4 cardiac toxicity excluding Grade 3 hypertension
- Non-sustained ventricular tachycardia (<30s) associated with syncope or pre-syncope
- Sustained ventricular tachycardia (≥30s) with or without symptoms
- Ejection Fraction (EF): ≥20% reduction in left ventricular ejection fraction (LVEF) to below the lower limit of normal (<50% on echocardiography)

Ophthalmic:

Part 1:

- 25% (or more) reduction on electroretinography (light and dark adapted) which does not resolve to baseline or 25% (or less) within 2 weeks following dose delay
- 50% (or more) reduction on electroretinography (light and dark adapted)

Part 2:

- 25% (or more) a- wave reduction on electroretinography (light and dark adapted) which does not resolve to baseline or 25% (or less) within 2 weeks following dose delay
- 50% (or more) a - wave reduction on electroretinography (light and dark adapted)
- 50% (or more) b- wave reduction on electroretinography (light and dark adapted) which does not resolve to baseline or 50% (or less) within 2 weeks following dose delay

***Note: If a patient is withdrawn from the study due to eye toxicity, ERG assessments will be repeated within 14 days and performed at least monthly thereafter until resolution or return to baseline. See Section 17.5 for further guidance.**

Other

- Grade 3 or 4 toxicity to organs other than the bone marrow including Grade 3 and 4 biochemical AEs and DLTs

EXCLUDING:

  - Grade 3 nausea
  - Grade 3 vomiting in patients who have not received optimal treatment with anti-emetics
  - Grade 3 diarrhoea in patients who have not received optimal treatment with anti-diarrhoeals
- Death
- Any drug related toxicity that causes interruption of treatment for >2 weeks (14 successive days). If a patient is deemed fit to restart treatment on the fifteenth day then this is not a DLT.

*** Note: In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia, a full blood count must be performed at least on Day 5 after the onset of the event to determine if a DLT has occurred. The Investigator must continue to monitor the patient closely until resolution to Grade 3 or less.**

Should any change be made to the grade or causality of an AE during the trial that may alter its DLT status, the CDD must be informed immediately as this may affect dose escalation decisions.

PLEASE NOTE: In the event of an Ophthalmic and/or Cardiac DLT (as defined above) these must be reported as a serious adverse event (SAE) to the CDD (see Section 10 for guidance on SAE reporting).

3.1.5 Definition of maximum tolerated dose

In Part 1 if two out of up to six evaluable patients at the same dose level experienced a DLT as defined in Section 3.1.4, the MTD was determined as the total daily dose level below. The MTD, was used to determine the RP2D following discussion of all the relevant safety, PK and PD data between CDD and the Investigators.

3.2 Patient evaluability

Part 1:

All patients that met the eligibility criteria and take at least one dose of AZD3965 were evaluable for safety decisions.

Patients who received less than 75% of their first continuous treatment cycle (for reasons other than toxicity) would not be evaluable for dose escalation decisions. Patients who completed 75% of their first continuous treatment cycle but did not complete the end of Cycle 1 ERG and ophthalmology assessments could also not be evaluable for dose escalation decisions. This was discussed on a per patient basis between the Investigator, Chief Investigator (CI) and CDD.

Part 2:

All patients that meet the eligibility criteria and take at least one dose of AZD3965 will be evaluable for safety decisions.

All patients who meet the eligibility criteria and take at least 75% of their first continuous treatment cycle (28 days) of AZD3965 and have a baseline assessment of disease will be evaluable for response.

To be assigned a status of complete response (CR) or partial response (PR), changes in tumour measurements must be confirmed by repeat measurements performed no less than four weeks after the response criteria are met. To be assigned a status of stable disease (SD), follow-up measurements must have met the SD criteria at least once and at least six weeks after the initial dose of the IMP AZD3965 is given.

[redacted]

3.3 Design of the clinical trial

This is a multi-centre, Phase I, dose escalation trial in two parts.

Part 1

In Part 1, a total of 42 patients with advanced solid tumours were recruited into Part 1 of the study, 40 of which received AZD3965.

At each dose level, up to six evaluable patients were treated on Day -7 followed by continuous daily dosing starting on Day 1. One treatment cycle was 28 days. In Part 1, Cycle 1 includes the additional dosing day at Day -7.

The starting dose was 5 mg given as an oral capsule. Pharmacokinetic assessments were performed during this cohort to assess the half-life of AZD3965 in order to inform whether dosing for future cohorts should be once or twice daily.

The next total daily dose level was planned to be 10 mg either once daily or split into two daily doses.

The total daily dose was doubled in successive cohorts until an NCI CTCAE Version 4.02 Grade 2 highly probably or probably related adverse drug reaction was reported. Subsequent dose increases between cohorts were up to a maximum of 50% driven by reported safety, PK and PD data. The decision to continue with dose escalations was based on drug exposure as measured by PK assessments during Cycle 1 and PD effects. Drug exposure did not exceed the maximum exposure limit as set out in Section 5.2. If PK data from Cycle 1 indicated that the exposure cap had been exceeded, the cohort would have been completed but no further dose escalations would have take place.

If continuous daily dosing was not tolerated at levels that inhibit MCT1 then intermittent schedules would be explored.

Up to six evaluable patients were treated at each dose level. [redacted] If a DLT was observed then the cohort was expanded to six patients. In the event of a gender specific DLT, at least one further patient of that gender would have been enrolled into an expanded cohort of at least six patients. If a second DLT was reported, a dose level below would have been expanded to six evaluable patients to identify the MTD.

An interval of 14 days (from Day -7 (7 days from Day 1) was observed between the recruitment of the first and second patients in a cohort. The second, third, fourth, fifth and sixth patients could be treated in parallel. Twenty-eight days (from Day 1) of data (safety, PK and PD) was available for a minimum of three evaluable patients in a cohort in order to make the decision to dose escalate. The following cohorts and doses were explored:

Cohort Number	**Dose**
1	5 mg once daily (OD)
2	10 mg OD
3	20 mg OD
4	30 mg OD
5	15 mg twice daily (BD)
6	10 mg BD

Part 2

In Part 2, up to 20 evaluable patients with DLBCL or BL will be treated at the RP2D from Part 1 of the study. There will be no administration of AZD3965 on Day -7 in Part 2 of the study. AZD3965 will be administered as continuous daily dosing in 28 day cycles starting from Cycle 1 Day 1 for up to six cycles. If the patient has not progressed after six cycles, further cycles may be given after discussion between the Investigator and the CDD and written approval given by the CDD, refer to Section 5.7. In the case of toxicity, treatment will be interrupted and then resumed when all toxicities have returned to Grade 1 or lower. Intermittent dosing schedules may be explored based on observed toxicities.

An interval of 14 days (from Cycle 1 Day 1) must be observed between the recruitment of the first and second patient in the expansion cohort but subsequent patients can be treated in parallel. Data must be available (safety and PK) for a minimum of three evaluable patients in order to make any decision to change the Part 2 dose (RP2D). Any changes to the Part 2 dose (RP2D) will be for safety reasons and to decrease the total daily dose only.

[redacted]

[redacted]

The study was designed in accordance with the EMEA Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products.

4 PATIENT SELECTION

4.1 Eligibility criteria

The patient must fulfil the eligibility criteria (listed in Sections 4.1.1 and 4.1.2).

4.1.1 Inclusion criteria:

1. Part 1:
    - Histologically or cytologically proven advanced solid tumour or Lymphoma, refractory to conventional treatment or for which no conventional therapy exists (if the diagnosis is confirmed by cytology and no follow-up historical tumour sample has been obtained, the patient will not be eligible).
    - Available archived tumour samples.

    Part 2:
    - Histologically proven DLBCL or BL, which is relapsed or refractory or both to conventional treatment or for which no conventional therapy exists or has been refused by the patient. (Refractory disease is defined as either progressive disease as the best response to the last line of systemic therapy or stable disease as the best response after at least two cycles of the last line of therapy with stable disease duration lasting no longer than six months from the last dose of the last line of systemic therapy. Relapsed disease is defined as disease that responded partially or completely to the last line of therapy and has since progressed).
    - Confirmed available tumour samples which can be obtained and used for the study to confirm MCT1 and MCT 4 expression (it is acceptable for the result to be reported after the patient has started study treatment) as demonstrated by IHC.
    - Measurable disease according to RECIST criteria version 1.1 or International Working Group criteria for Lymphoma
2. Life expectancy of at least 12 weeks
3. World Health Organisation (WHO) performance status of 0 or 1 (Appendix 1)
4. Haematological and biochemical indices within the ranges shown below.

Laboratory Test	**Value required (For both Parts 1 and 2 except where specified)**
Haemoglobin (Hb)	≥9.0 g/dL (90 g/L) or ≥10.0 g/dL (100 g/L) if transfusion within last 4 weeks
Absolute neutrophil count (ANC)	**Part 1:** ≥ 1.5 x 10^9/L **Part 2:** ≥ 1.0 x 10^9/L
Platelet count	**Part 1:** ≥ 100 x 10^9/L **Part 2:** ≥ 50 x 10^9/L
Serum bilirubin	≤ 1.5 x upper limit of normal (ULN)
Alanine amino-transferase (ALT), aspartate amino-transferase (AST) and alkaline phosphatase (ALP)	≤ 2.5 x ULN or ≤ 5 x ULN in presence of liver metastases (ALP ≤ 5 x ULN in presence of bone metastases)
GFR	

Either: Calculated creatinine clearance (using the Wright or Cockcroft-Gault formula) Or: Isotope clearance measurement (uncorrected)	≥ 50 mL/min
Prothrombin time (PT)	<1.5 x ULN
Glucose (fasting)	<7.8 mmol/L
Lactate	Between 0.5 and 2.5 mmol/L inclusive
Bicarbonate	Between 22 mmol/L and 1.5 x ULN inclusive

5. LVEF>50%
6. 18 years or over
7. Written (signed and dated) informed consent and be capable of co-operating with treatment and follow-up

4.1.2 Exclusion criteria:

1. Radiotherapy (except for palliative reasons), endocrine therapy, immunotherapy or chemotherapy during the previous four weeks (six weeks for nitrosoureas, Mitomycin-C and 4 weeks for investigational medicinal products) before treatment.[5] Shorter wash out periods may be acceptable if patient has recovered from therapy related toxicity and is at least five terminal half-lives post last administration. This should be discussed and agreed with the CDD and CI.
2. Ongoing toxic manifestations of previous treatments greater than NCI CTCAE Grade 1 at the time of starting study treatment. Exceptions to this are alopecia or certain Grade 2 toxicities, which in the opinion of the Investigator and the CDD should not exclude the patient.
3. Symptomatic brain or leptomeningeal metastases.
4. Patients with known retinal disease or macular degeneration affecting visual acuity as assessed by ophthalmologic tests.
5. Female patients who are able to become pregnant (or are already pregnant or lactating). However, those patients who have a negative serum or urine pregnancy test before enrolment and agree to use two forms of contraception (one highly effective form plus a barrier method) [oral, injected or implanted hormonal contraception and condom; intra-uterine device and condom; diaphragm with spermicidal gel and condom] or agree to sexual abstinence, effective from the first administration of AZD3965, throughout the trial and for six months afterwards are considered eligible.[6]
6. Male patients with partners of child-bearing potential (unless they agree to take measures not to father children by using a barrier method of contraception [condom plus spermicide] or to sexual abstinence effective from the first administration of AZD3965, throughout the trial and for six months afterwards. Men with partners of child-bearing potential must also be willing to ensure that their partner uses an effective method of contraception for the same duration for example, hormonal contraception, intrauterine device, diaphragm with spermicidal gel or sexual abstinence). Men with pregnant or lactating partners must be advised to use barrier method contraception (for example, condom plus spermicidal gel) to prevent exposure of the foetus or neonate.[6]
7. Any major surgery in the preceding eight weeks prior to the start of treatment or major thoracic or abdominal surgery from which the patient has not yet recovered
8. Patients who are unable to swallow oral medication.
9. Alterations to corticosteroid dose within 2 weeks prior to first dose of AZD3965. An exception to this is usage of prednisolone or an equivalent steroid which is acceptable during screening but must be stopped at least 72 hours days prior [redacted]
10. Gastrointestinal disorders likely to interfere with absorption of the study drug (e.g. partial bowel obstruction or malabsorption).
11. At high medical risk because of non-malignant systemic disease including active uncontrolled infection.
12. Known to be serologically positive for hepatitis B, hepatitis C or human immunodeficiency virus (HIV). (N.B. Mandatory testing not required).
13. History of serious allergy or auto-immune disease.
14. Diabetes mellitus treated with oral anti-diabetic medication (patients with diet controlled or insulin controlled diabetes may be included with fasting glucose <7.8 mmol/l and normal HbA1c).
15. Cardiac conditions as follows:
    - Clinically significant cardiovascular event within 6 months prior to study entry to include:
      a. Acute coronary syndrome (myocardial infarction or unstable angina)
      b. congestive heart failure requiring therapy;

[5] Baseline measurements must be performed within four weeks before the patient receives the first dose. The interval between the last anti-cancer therapy and these measurements must be at least four weeks (28 days). Shorter wash out periods may be acceptable if patient has recovered from therapy related toxicity and is at least five terminal half-lives post last administration. This should be discussed and agreed with the CDD and CI.

[6] Abstinence is only considered to be an acceptable method of contraception when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

- Severe valvular heart disease (as defined by British Society of Echocardiography – see Appendices 6)
- Presence of an atrial or ventricular arrhythmia, other than atrial fibrillation with well controlled ventricular rate, for which treatment is indicated (anti-arrhythmic drugs or implantable cardioverter defibrillator)[7]
- Second degree Mobitz type 1 (Wenckebach) heart block with symptoms, or second degree Mobitz type 2 or third degree heart block with or without symptoms, are exclusions unless the patient has a functional pacing system[7]
- QTc > 450 msec in adult male and > 460 msec in adult females (QTc to be verified manually (QTcF correction))
- History of congenital long QT syndrome
- History of Torsade de Pointes (TdP) (or any concurrent medication with a known risk of QT prolongation) – See Appendix 3for further details
- Uncontrolled hypertension (BP ≥ 160/100mmHg despite medical therapy)

16. Patients who have had extensive radiotherapy to greater than 25% of bone marrow within 8 weeks. Prior autologous bone marrow transplant will not exclude a patient
17. Is a participant, or plans to participate in another interventional clinical trial, whilst taking part in this Phase I study of AZD3965. Participation in an observational trial or interventional clinical trial which does not involve administration of an IMP would be acceptable.
18. Any other condition which in the Investigator's opinion would not make the patient a good candidate for the clinical trial.
19. <u>For Part 2 only:</u> Current malignancies of other types, with the exception of adequately treated cone-biopsied *in situ* carcinoma of the cervix uteri; basal or squamous cell carcinoma of the skin; and patients with low risk prostate cancer on surveillance (with a Gleason score of ≤6 and a PSA of ≤10)

4.2 Patient enrolment

Before enrolling the patient in the trial, the Investigator or designated representative should determine the eligibility of the patient during the trial screening period. This determination must be clearly documented in the patients' hospital records.

Eligible patients must be enrolled in the electronic data capture (EDC) system by site staff and then registered at the CDD before they start treatment with AZD3965. If the patient is eligible for the trial, then a patient number will be automatically allocated by the EDC system during the enrolment process. The CDD will send confirmation of the patient registration including the assigned dose level to the Investigator following enrolment of the patient. Study treatment may only be administered after confirmation has been received.

5 TREATMENT

5.1 Selection of the Phase I starting dose and schedule (Part 1)

The starting dose was 5 mg given as a capsule once daily.

The justification for the starting dose can be found in Section 2.2.7

5.2 Maximum Exposure Limit

[redacted]

[redacted]

5.3 Dosing schedule/treatment schedule (Parts 1 and 2)

For Part 1 of the study, AZD3965 was administered orally on Day -7 and then continuously for a 28 day cycle starting on Day 1.

For Part 2 of the study, AZD3965 will be administered orally continuously for a 28 day cycle starting on Cycle 1 Day 1. There will be no administration of AZD3965 on Day -7 in Part 2 of the study.

In Part 1, the total daily dose was initially administered once daily and was reviewed throughout Part 1, the total daily dose was spilt into a twice daily dosing schedule.

In both Part 1 and 2 a maximum of six cycles will be administered (further cycles can be given upon review of the data and approval by CRUK CDD where patients are benefiting from receiving AZD3965 i.e. tumour assessments show a stable or partial/complete response, refer to Section 5.7).

The AZD3965 capsules must be swallowed whole (with water) and not chewed, crushed, dissolved or divided.

Patients in Part 1 were instructed to take AZD3965 with food, except for their first dose at Day -7 which was taken fasted. In Part 2 as there is no Day -7 dose, AZD3965 is to be taken with food and should be taken at the same time(s) every day.

For the once daily dosing in Part 1, the total daily dose of AZD3965 was taken at the same time once a day, and for twice daily dosing, the total daily dose of AZD3965 was spilt into two doses and should be taken in the morning and 12 hours later, respectively.

In Part 2 a twice daily dosing is planned unless emerging data suggests a once daily dosing is indicated.

On the days of PK sampling (see Section 9.4.1) patients should take their scheduled dose at the hospital so that the exact time of administration can be recorded.

In cases of toxicity, treatment may be interrupted and then resumed when all toxicities have returned to Grade 1 or lower. In the event of Grade 3 or 4 QTc prolongation (QTc interval >500 msecs or increase of > 60 msecs from baseline (QTcF correction)), treatment with AZD3965 will be withdrawn.

Intermittent dosing schedules and administration with or without food may be explored based on observed toxicities or if continuous daily dosing is not tolerated at levels that inhibit MCT1.

5.4 Dose escalation scheme (Part 1)

Each patient cohort included a maximum of six evaluable patients following a rolling six dose escalation scheme (Skolnik A.M. *et al.*, 2008).

The starting dose was 5 mg given as an oral capsule. 5, 10, 20, and 30 mg capsules can be manufactured. Pharmacokinetic assessments were performed during this cohort to assess the potential half-life of AZD3965 in order to inform whether dosing for future cohorts should be once or twice daily. The next total daily dose level will be 10 mg either once daily or split into two daily doses.

The total daily dose was doubled in successive cohorts until an NCI CTCAE Version 4.02 Grade 2 highly probably or probably related adverse drug reaction was reported. Subsequent dose increases between cohorts was up to a maximum of 50% driven by reported safety, PK and PD data. If continuous daily dosing is not tolerated at levels that inhibit MCT1 then intermittent schedules will be explored.

A maximum of six evaluable patients were treated at each dose level with at least one male patient in each cohort. It is acceptable that the fourth, fifth and sixth patients can begin treatment at the same time as the second and third patients which must be after the first patient has completed Cycle 1 Day 7 of treatment although this will be assessed and confirmed by the CDD based on emerging data from the study.

The dose level of AZD3965 was assigned according to the number of patients already enrolled at the current dose level, the number of DLTs (and any other drug-related AEs) observed at the current dose level and the number of patients enrolled who are at risk of developing a DLT (see Section 3.2 Definition of dose limiting toxicity). When sufficient data, as deemed by the Sponsor and CI, was available to assess these, the AZD3965 dose level was assigned according to the following:

- If the data is available from a minimum of three patients who have been treated in a cohort and no DLTs have been observed at that dose level, then dose escalation can be considered.

- If the data is available from three patients who have been treated in a cohort and one DLT has been observed at that dose level, then the cohort will be expanded to include at least 6 patients.

- If two DLTs have been observed at any dose level, the dose will be de-escalated and the previous total daily dose level will be expanded to include up to six patients. If the previous total daily dose level already included a cohort of six patients then this will be identified as the MTD. If a patient has already started treatment at a higher dose level at the time when two DLTs are identified at a lower dose level, their dose will be assessed and confirmed by the Sponsor based on the reported safety data.

- If not all data are available from at least three patients in order to take a decision on dose escalation but an eligible patient is ready to begin treatment, the dose level will remain the same. Up to six patients may be enrolled at that dose level.

Twenty-eight days of data (safety and PK) should be available for a minimum of three evaluable patients in a cohort in order to make the decision to dose escalate.

The decision to continue with dose escalations was guided by drug exposure. Assessments of drug exposure was based on Day -7, Day 1 and Day 29 PK from Part 1 only. Drug exposure was not to exceed the maximum exposure limit as set out in Section 5.2. If PK data from any of these time points indicated that the exposure cap has been exceeded, the cohort would be completed (toxicity permitting) but no further dose-escalations will take place.

5.4.1 Intra-patient dose escalations

No intra-patient dose escalation is allowed.

5.4.2 Expansion of dose level(s)

If one instance of DLT (as defined in Section 3.1.3) was observed in three patients, at least six evaluable patients would be treated at that dose level. If one out of six patients experienced a DLT, dose escalation would continue. If two out of up to six (i.e. between two and six) patients experience a DLT dose escalation would stop and this dose would be defined as the maximum administered dose (MAD). At least six patients would be treated at the total daily dose level below the MAD to define the MTD.

The MAD could also equal the MTD in the event that dose escalation was stopped before two DLTs were observed at a given dose level, due to the expectation that higher dose levels would be too toxic to administer to patients.

5.5 Dose modifications

5.5.1 Dose withdrawal

In the event of CTCAE Grade 3 or 4 QTc prolongation (QTc interval >500 msecs or increase of >60 msecs from baseline (QTcF correction)) treatment with AZD3965 will be withdrawn.

5.5.2 Dose reductions

In Part 1 the dose of AZD3965 would be reduced to the previous dose level for any patient who experienced a DLT (with the exception of QTc prolongation, these patients would be withdrawn from the trial, see Section 5.5.1). If a patient had a dose reduction, their dose would not be re-escalated.

Treatment at the reduced dose would start when the toxicities had resolved to Grade ≤1 or returned to baseline (if within 14 days).

If the patient experienced the same or different DLT toxicity again at this reduced dose, there would be no further dose reductions and the patient was withdrawn from the study.

In Part 2, the PK profile of AZD3965 and patient safety data will be reviewed after the first three evaluable patients. Following this review, the RP2D may switch to once or twice daily dosing (at the same total daily dose level) or a lower total daily dose at the discretion of the CDD and CI. Any DLTs experienced during Part 2 will be collected to assist with assessment of patient safety profiles and the RP2D may be adjusted accordingly.

5.5.3 Dose delays

In the event of toxicity, treatment should be delayed for up to two weeks until these toxicities have resolved to Grade ≤1 or returned to baseline. If there is no recovery after a two week delay, the patient should be withdrawn from the trial.

Intermittent dosing schedules may be explored based on observed toxicities, PK and PD data.

5.6 Missed Doses

Patients should take the correct number of AZD3965 capsules at the same time(s) every day.

Should a patient miss a scheduled dose in error, for example, forgetting to take the drug, then AZD3965 may be administered up until 12 hours after the scheduled dosing time (this applies to once a day dosing only). If it is not taken within this time then the patient should wait until the next scheduled dose and continue as per normal drug administration.

If the dosing schedule is twice daily dosing and the patient should miss a dose in error, then AZD3965 may be administered up until two hours after the scheduled time of dose. If it is not taken within this time then the patient should wait until the next scheduled dose and continue as per normal drug administration. Any missed doses should be recorded in the patient diary card.

An occasional shift in dosing may be permitted by CDD, to accommodate study visits and study assessments. This must be discussed and agreed in advance. On these occasions dosing should be brought back to the original dosing schedule as soon as possible.

Should a patient vomit after taking the drug, then the patient should be instructed not to take another capsule until their next scheduled dosing time.

5.7 Duration of treatment

Treatment should continue for six cycles unless (a) the patient asks to be withdrawn, (b) there is evidence of disease progression (c) the patient is experiencing unacceptable toxicity or (d) the Investigator feels the patient should be withdrawn from any other reason including those listed in Section 12.

If a patient is benefiting from treatment with AZD3965 (i.e. has stable or responding disease as measured by RECIST version 1.1 or International Working Group criteria for Lymphoma) and the patient is not experiencing any Grade 2 or greater drug-related AEs then the CI and / or Principal Investigator (PI) can ask the CDD if the patient can continue with treatment. The CDD will request a full toxicity profile of that patient when considering the request. Should the decision be to allow further treatment, 6 further cycles may be given. After completion of 12 cycles, a further review will be conducted by the Sponsor, CI and treating clinician(s). A patient may continue on study as long as they are benefiting from treatment with AZD3965 and IMP stock is available. If the CDD decides not to allow the patient to

continue treatment, based on the information provided or on other information received, then the CDD's decision is final.

For the purposes of this trial a patient who completes six or more treatment cycles is considered to have completed the trial.

For patients who continue on study for extended treatment, i.e. for longer than 6 or 12 cycles, these patients must continue to show that benefit is being derived from receiving AZD3965. After each disease assessment the PI will relay findings to CDD for this determination to be met.

5.7.1 Replacement of patients

In **Part 1**, patients were replaced if they fulfilled the following criteria and three evaluable patients had not yet been treated at the same dose level:

- Patients who miss more than 25% of their first AZD3965 cycle (for reasons other than drug related toxicity).

Patients who missed more than 50% of their first AZD3965 cycle due to toxicity which was not dose limiting were discussed between the CDD and CI and a decision will be taken on whether the patient should be replaced by another at the same dose level.

Patients could be replaced if they were unable to complete [redacted] the end of Cycle 1 ERG and ophthalmology assessments. The decision as to whether to replace such a patient depended on the status of the other patients within that cohort [redacted] ERG data already obtained at that dose level. This decision was made by the CDD in consultation with the CI.

In **Part 2**, patients will be replaced in this phase if they fulfil the following criteria:

- Patients who miss more than 25% of their first AZD3965 cycle (for reasons other than drug related toxicity).

Patients who complete more than 75% of their first AZD3965 cycle (for reasons other than drug related toxicity) but fulfil one of the following additional criteria may also be replaced in Part 2. This will be discussed on a per patient basis between the Investigator, CI and CDD.

- [redacted]
- [redacted]

5.8 Concomitant medication and treatment

Concomitant medication may be given as medically indicated. Details (including doses, frequency, route and start and stop dates) of the concomitant medication given must be recorded in the patient's medical records but only the medication name, start date and stop date is required to be entered into the electronic case report form (eCRF).

Radiotherapy may be given for the control of bone pain; however this cannot be given concomitantly during AZD3965 administration. Please note that in exceptional circumstances, if the patient's radiotherapy cannot be completed within a two week period, this may be extended to three weeks after consultation with CDD. Irradiated lesions will not be evaluable for response.

The patient must not receive other anti-cancer therapy or investigational drugs while on the trial.

Patients may continue the use of bisphosphonates for bone disease and corticosteroids provided the dose has not been changed in the two weeks prior to administration of the first dose of AZD3965 and is not altered during the first 15 days post administration of AZD3965 on Day 1.

For patients who require prednisolone (or equivalent) for a short duration to improve their quality of life during screening, this is acceptable, [redacted]

The concomitant administration of potent CYP3A inhibitors, specifically: protease inhibitors (atanazavir, indinavir, nelfinavir, ritonavir, saquinavir), macrolide antibiotics (clarithromycin, telithromycin), azole antifungals (ketoconazole, itraconazole, voriconazole), nefazodone should be avoided.

The concomitant administration of CYP3A inducers, specifically: rifampicin, rifapentine, rifabutin, phenytoin, carbamazepine, phenobarbitol, St John's Wort should also be avoided.

An up to date list of CYP3A inhibitors and inducers can be found at https://drug-interactions.medicine.iu.edu/Clinical-Table.aspx.

Drugs with a known risk of inducing TdP should not be taken during the trial. These drugs (see Appendix 3) have been sourced from https://www.crediblemeds.org. As drugs are reviewed on an ongoing basis to assure that the available evidence supports their continued placement on this list, the list changes regularly. **Therefore, check the website at crediblemeds.org for the most up-to-date information.** If these drugs are to be used in an emergency once the patient is off AZD3965 treatment, they should be taken a minimum of 24 hours after the patient's last dose of AZD3965. Before a patient re-starts AZD3965 treatment, a maximum of 5 half-lives of the concomitant drug must be reached.

If a patient is taking any dietary supplements or complementary medicines/botanicals, the CDD must be informed at the earliest opportunity.

Use of potential prohibited concomitant medications will be discussed on a patient by patient basis with the CDD and CI before a patient is enrolled on the study.

6 PHARMACEUTICAL INFORMATION

6.1 Supply of AZD3965

A complete certificate of analysis and a Qualified Person (QP) certification must be supplied with each shipment of AZD3965 and be retained in the Pharmacy File.

For information on AZD3965 and re-ordering of supplies, contact the Clinical Research Associate (CRA)/Clinical Study Manager (CSM) responsible for the trial who will arrange further supplies.

AZD3965 will be supplied by:

[redacted]

Fisher Clinical Services (UK) Limited must send confirmation of shipment to the CRA/CSM once AZD3965 has been despatched to the clinical trial site.

The primary packaging for AZD3965 will be labelled according to Eudralex Volume 4: Annex 13 'Investigational Medicinal Products' of the European Union guide to Good Manufacturing Practice (GMP). An example of the label can be found in the Pharmacy file.

6.2 Pharmaceutical data

6.2.1 Formulation of AZD3965

[redacted]

[redacted]

6.2.2 Storage conditions

All supplies must be stored in a secure, limited access storage area. AZD3965 must be stored at ambient temperature between 15°C and 30°C.

AZD3965 must be stored in its original bottle with the cap on tightly. Study medication must not be refrigerated. Please refer to the current Investigator's Brochure (IB) for detailed information on storage conditions and stability.

Patients must ensure that AZD3965 is kept out of sight and reach of children.

6.2.3 Stability of AZD3965

Please refer to the label on the bottle (primary package) for the expiry date of the unopened AZD3965.

Opened bottles of AZD3965 MUST NOT be refrigerated. Bottles must be stored between 15°C and 30°C and must be kept out of sight and reach of children. Opened bottles of AZD3965 that have passed the expiry date stated on the bottle must be returned to the pharmacy. Patients must close the cap of the bottle tightly immediately after dispensing the number of capsules they are required to take.

Please refer to the current Investigator Brochure for detailed information on storage conditions and stability

6.2.4 Dispensing of AZD3965

Sufficient capsules of AZD3965 must be dispensed on each occasion to cover the prescribed dose over the period to the next scheduled dispensing.

6.2.5 AZD3965 administration

The AZD3965 capsules must be swallowed whole (with water) and not chewed, crushed, dissolved or divided.

AZD3965 should be taken as directed with food. For once daily dosing AZD3965 should be taken at the same time every day and for twice daily dosing AZD3966 should be taken in the morning and 12 hours later.

Should a patient miss a scheduled dose in error, for example, forgetting to take the drug, then AZD3965 may be administered up until 12 hours after the scheduled dosing time (this applies to once a day dosing only). If it is not taken within this time then the patient should wait until the next scheduled dose and continue as per normal drug administration.

If the dosing schedule is twice daily dosing and the patient should miss a dose in error, then AZD3965 may be administered up until two hours after the scheduled time of dose. If it is not taken within this time then the patient should wait until the next scheduled dose and continue as per normal drug administration.

An occasional shift in dosing may be permitted by the CDD to accommodate study visits and study assessments. On these occasions dosing should be brought back to the original dosing schedule as soon as possible.

If the patient vomits after taking the AZD3965 capsule, the patient should not take another capsule and should wait for the next scheduled dose.

On the days of PK sampling (see Section 9.3) patients should take their scheduled dose (morning dose if twice daily dosing) at the hospital so that the exact time of administration can be recorded.

6.3 AZD3965 accountability

Accurate records of AZD3965 shipments received, capsules dispensed, and returned must be maintained. This inventory record must be available for inspection at any time by CRAs or CSMs of the CDD. AZD3965 supplies are to be used only in accordance with this protocol and under the supervision of the Investigator.

Patients will be asked to complete a patient diary to document drug administration and to return the bottle and any remaining capsules at each visit. The Investigator should make every effort to ensure patients' compliance to treatment.

The Investigator undertakes not to destroy any unused AZD3965 unless directed to by CDD staff. Any unused capsules must be destroyed according to hospital procedures and properly accounted for using the IMP Destruction Form (when instructed to do so) and also on the IMP Accountability Record. During the course of the trial the CRA will check the numbers of bottles of capsules of AZD3965 shipped to the centre, the number used and the number destroyed or returned. The pharmacy will give an account of any discrepancy.

7 INVESTIGATIONS SCHEDULE FOR PART 1 OF THE STUDY

RECRUITMENT TO PART 1 OF THE STUDY IS NOW CLOSED

For details of investigations performed in Part 1 of this clinical trial, please refer to Protocol V 12.0 dated 22Aug2018 which still includes the details from this part of the trial.

8 INVESTIGATIONS SCHEDULE FOR PART 2 OF THE STUDY

In cases where a patient has investigations at a different hospital, for example weekly blood samples, then it is the Investigator's responsibility to ensure he/she receives and reviews the results in a timely manner. The results must be recorded on the eCRF and the reports from the other hospitals must be available for source data verification. Laboratory reference ranges, including effective dates, and evidence of laboratory accreditation must be obtained from all laboratories used.

8.1 Pre-treatment evaluations

Details of all evaluations/investigations for enrolled patients, including relevant dates, required by the protocol must be recorded in the medical records so that the eCRF can be checked against the source data.

Please also refer to the tabulated Schedule of Assessments for Part 2 of the study in Section **Error! R eference source not found.**.

8.1.1 Obtaining written informed consent

Written informed consent must be obtained from the patient before any protocol-specific procedures are carried out.

The patient must be given adequate time to think about their commitment to the study. If more than 28 days has passed since informed consent was obtained before the start of AZD3965 dosing then the Investigator should consider whether repeat consent should be obtained from a patient.

Consent for analysis of initial historical archived or (if historical tissue not available) fresh (new) screening tumour sample for MCT1 and MCT4 IHC profiling must be obtained prior to analysis of the sample for the trial and should be obtained pre-screening or at the time of full trial consent. Analysis of the sample can occur in parallel to screening and the result does not need to be confirmed before the patient enrols onto the study.

Only the Principal Investigator (PI) and those Sub-Investigator(s) delegated responsibility by the PI, and have signed the Delegation Log, are permitted to gain informed consent from patients and sign the consent form. All signatures must be obtained before the occurrence of any medical intervention required by the protocol (ICH GCP 4.8.8 and 8.3.1.2). The patient should sign and date the consent form in the presence of the Investigator, followed by the Investigator signature. The date of the signatures of both the patient and the PI/Sub-Investigator should be the same.

The PI or the Sub-Investigator must inform the patient about the background to, and present knowledge of the normal management of their disease and the AZD3965 and must also ensure that the patient is aware of the following points.

- The known toxicity of AZD3965 and the possibility of experiencing side-effects.
- That AZD3965 is new and that the exact degree of activity is at present unknown, but that treating him/her will contribute to further knowledge.
- The potential dangers of becoming pregnant (or the patient's partner becoming pregnant) and he/she has been given information about appropriate medically approved contraception (refer to Section 10.7).
- That he/she may refuse treatment either before or at any time during the trial and that refusal to participate will involve no penalty or loss of benefits to which they are otherwise entitled.
- Whom to contact for answers to pertinent questions about the research and their rights, and also who to contact in the event of a research-related injury.

A copy of the consent form and patient information sheet must be given to the patient to keep and the original consent form and patient information sheet, must be filed in the Investigator Trial File (ITF) (unless otherwise agreed that the original consent form will be filed in the medical records and the copies kept in the ITF).

8.1.2 Pre-screening

The following should be performed/obtained **within six months before** the patient receives the first dose.

- Written informed consent (as detailed in Section **Error! Reference source not found.**).
- Confirmation that tumour samples are available and can be used for the study to confirm MCT1 and MCT 4 expression as demonstrated by IHC either during pre-screening, screening or once the patient is enrolled on the study.

All patients in Part 2 should give separate written consent before analysis of historical or fresh (new) screening tumour biopsy sample taken for MCT1 and MCT4 IHC profiling.

Historical tumour biopsy samples can be used if they were obtained more than 6 months prior to Day 1. However, it's preferred that fresh (new) samples are used to provide a more accurate result.

For those patients where a historical tumour biopsy sample is not available or the MCT1 and MCT4 IHC profiling is inconclusive and the patient hasn't yet been enrolled on to the study, a fresh (new) screening tumour biopsy will be preferred. The fresh (new) screening sample tumour biopsy must be performed/obtained **within eight weeks before** the patient receives the first dose.

8.1.3 Evaluations within four weeks prior to first dose (Day -28 to Day -1)

The following should be performed/obtained **within the four weeks before** the patient receives the first dose.

- Written informed consent (as detailed in Section 8.1.1);
- Demographic details;
- Medical history including prior diagnosis, prior treatment, concomitant diseases and concomitant treatment;
- [redacted]

[redacted]

- Radiological disease assessments: Radiological measurements (chest computerised tomography (CT) scan of neck, chest, abdomen and pelvis, FDG-PET/CT for those patients with PET-avid disease (as applicable) magnetic resonance imaging (MRI), bone scan (as applicable) – must be performed **within four weeks before** the patient receives the first dose.

Note that all adverse events (AEs), including serious adverse events (SAEs), must be monitored and recorded in the eCRF from the time the patient consents to any protocol-specific procedure (see Section 10 for further details).

8.1.4 Evaluations within two weeks prior to first dose (Day -14 to Day -1)

The following should be performed **within the two weeks before** the patient receives the first dose:

- Serum or urine human chorionic gonadotropin (HCG) test to rule out pregnancy at trial entry; results must be obtained and reviewed before the first dose of the AZD3965 is taken, if applicable (i.e. women of child bearing potential);
- Echocardiogram (ECHO);
- Ophthalmic test: Best corrected visual acuity;

- Pattern electro-retinography (pERG) and full-field electro-retinography (ffERG) (light and dark adapted) (or equivalent ERG assessment as previously agreed with the CDD).

8.1.5 Evaluations within one week prior to first dose (Day -7 to Day -1)

The following should be performed **within one week before** the patient receives the first dose:

- Clinical disease measurements, if applicable (i.e. patients with clinically assessable disease);
- Tumour serum markers (if applicable);
- Complete physical examination;
- WHO performance status;
- Weight and temperature;
- Seated blood pressure (BP) and pulse rate;
- Chest X-ray (CXR); If the baseline CT/MRI scan included the thorax, a CXR may not be necessary provided all windows are presented for review.
- Laboratory tests (blood/urine samples) to confirm eligibility (see section 4.1.1 for required values):
    - Haematology – haemoglobin (Hb), white blood cells (WBC) with differential count (neutrophils, lymphocytes, monocytes, reticulocytes) and platelets
    - Biochemistry – sodium, potassium, adjusted calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), glucose (**fasting at baseline to confirm eligibility and then non-fasting at subsequent timepoints**. If non-fasting result is ≥7.8mmol/l fasting glucose should be repeated), lactate and bicarbonate (at baseline [screening] to confirm eligibility and Cycle 1 Day 1 only).
    - Urinalysis – pH, specific gravity, glucose, protein, blood, ketones
    - Coagulation – PT (screening only)
- Cardiac Troponin T or I;
- Electrocardiogram (ECG); including measurement of QTc and verified manually (QTcF correction). ECG traces must be checked by an attending physician, consultant or specialist registrar, at the time of generation. A comment confirming normal/abnormal must be added along with a signature and date on the ECG to confirm review (abnormal ECGs to be reviewed by a Cardiologist prior to patient registration);
- [redacted]

[redacted]

8.2 Evaluations on Cycle 1 Day 1 (+/- 24 hours)

- Administration of first dose of AZD3965;
- Blood tests to include bicarbonate and lactate: See section 8.1.5 (blood to be taken after first dose);

- Blood [redacted] for PK [redacted]
- [redacted]
- [redacted]

[redacted]

8.3 Evaluations at 24 hours (± 2 hours) after the first dose of AZD3965 treatment

- Cardiac Troponin T or I; to be repeated at 48 +/-2 hours post-dose;
- ECGs (including measurement of QTc and verified manually (QTcF correction);

  ECG traces must be checked by an attending physician, consultant or specialist registrar, at the time of generation. A comment confirming normal/abnormal must be added along with a signature and date on the ECG to confirm review. Abnormal ECGs to be reviewed by a Cardiologist prior to dosing;
- [redacted]

8.4 Evaluations during continuous AZD3965 treatment Cycles 1–12 <u>(excluding Cycle 1 Day 1)</u>

(See Section 8.2 for Cycle 1 Day 1 and Section 8.5 for Cycle 13 onwards)

- Adverse events and concomitant treatments: At each visit an assessment of any AE experienced since the previous visit must be made by the Investigator or Research Nurse and the start and stop dates of the AE together with the relationship of the event to treatment with AZD3965 must be recorded in the medical records. All AEs must be graded according to NCI CTCAE Version 4.02. Any concomitant treatment must also be recorded in the medical records and in the eCRF (see Section 10 for further details regarding AE reporting requirements);
- Physical examination: When clinically indicated, a symptom-directed physical examination will be performed weekly during the first cycle and on the first day of each cycle in subsequent cycles (±1 day). N.B. Dermatological assessment to include questioning on genital skin changes or sores and experience of testicular pain in male patients;
- WHO performance status and weight on the first day of each cycle (±1 day);
- Temperature, seated BP and pulse rate every week in Cycle 1 and 2, and every 2 weeks thereafter (±1 day);
- Laboratory tests (blood/urine) must be repeated weekly in Cycle 1 and 2, and every 2 weeks thereafter (±1 day): see Section8.1.5;
- ECGs (include measurement of QTc and verified manually (QTcF correction)): weekly in Cycle 1 and 2, and every 2 weeks thereafter (±1 day);

  ECG traces must be checked by an attending physician, consultant or specialist registrar, at the time of generation. A comment confirming normal/abnormal must be added along with a signature and date on the ECG to confirm review. Abnormal ECGs to be reviewed by a Cardiologist prior to dosing.
- Cardiac Troponin T or I: weekly in Cycle 1 and 2, and every 2 weeks thereafter (±1 day);

- Questionnaire for eye toxicity: weekly in Cycle 1 (±1 day). If the patient reports any changes in their vision, Ophthalmic tests listed in the bullet point below and ERG assessments should be performed (as per the 'Management of eye toxicity' appendix 4);

- Ophthalmic test: Best corrected visual acuity. To be conducted on the first day of each cycle (±3 days);

  If a reduction or changes are identified on the ophthalmic test, ERG should be performed immediately (refer to Appendix 4 Management of eye toxicity);

- Pattern and full-field ERG (light and dark adapted) (or equivalent ERG assessment as previously agreed with the CDD) to be performed at the end of Cycle 1 ±3 days and then repeated every 28±3 days if the patient reports symptoms of eye toxicity/changes in their vision. **ERGs can be stopped after the end of Cycle 1 if no symptoms are reported and the Ophthalmologist agrees no further ERG testing is required**;

- Assessment of disease (radiological, clinical – if applicable, and tumour markers): This must be repeated at the end of every 2 cycles (±3 days) unless assessment has been performed within the previous 4 weeks (28 days).

PLEASE NOTE: If patient presents with disease progression, assessment of tumour disease should be performed at the last study visit unless assessment has been performed within the previous four weeks (28 days). **If assessment is to be conducted on Cycle 1 Day 29 (or Day 1 Cycle 2), assessment must be performed prior to the fresh (new) on study paired tumour biopsy.**

- Blood [redacted] PK assays: see Section 9.

[redacted]

- [redacted]
- [redacted]
- [redacted]

8.5 Evaluations from Cycle 13 onwards

From Cycle 13 onwards, the patient will attend the study site on Day 1 of each cycle. A telephone call or on-site visit on Day 15 will be conducted if deemed required (either by site staff or by the patient).

PLEASE NOTE: Abnormal or out of range laboratory results from tests carried out on Day 1 will require an onsite visit or telephone call on Day 15 to ensure continuing patient safety and well-being is reviewed during the treatment cycle.

The frequency of the following investigations may be adjusted (increased or decreased) if clinically indicated or deemed required by the Investigator.

At each study visit:

- Adverse events and concomitant treatments: At each visit an assessment of any AE experienced since the previous visit must be made by the Investigator or Research Nurse and the start and stop dates of the AE together with the relationship of the event to treatment with AZD3965 must be recorded in the medical records. All AEs must be graded according to NCI CTCAE Version 4.02. Any concomitant treatment must also be recorded in the medical records and in the eCRF (see Section 10 for further details regarding AE reporting requirements).
- AE assessments must include any visual changes which should be managed as per Section 10.

On the first day of each cycle (±1 day):

- Physical examination: When clinically indicated or deemed required by the Investigator, a symptom-directed physical examination will be performed. N.B. Dermatological assessment to include questioning on genital skin changes or sores and experience of testicular pain in male patients.
- WHO performance status and weight.
- Temperature, seated BP and pulse rate. *May be conducted at Cycle Day 15 (±1 day) if onsite visit.*
- Laboratory tests (blood/urine); see Section 8.1.5. *May be conducted at Cycle Day 15 (±1 day) if onsite visit.*

Every 3 cycles (±3 days):

- Assessment of disease (radiological, clinical – if applicable, and tumour markers): This must be repeated at the end of every 3 cycles (±3 days) unless assessment has been performed within the previous 4 weeks (28 days).

  PLEASE NOTE: If patient presents with disease progression, assessment of tumour disease should be performed at the last study visit unless assessment has been performed within the previous four weeks (28 days).

- Opthalmic test: Best corrected visual acuity. To be conducted on the first day of every third cycle (±3 days).
  If a reduction or changes are identified on the ophthalmic test, ERG should be performed immediately (refer to Appendix 4 Management of eye toxicity).

- Pattern and full-field ERG (light and dark adapted) (or equivalent ERG assessment as previously agreed with the CDD).

Every 6 cycles (±3 days):

- Echocardiogram (ECHO) – *may also be performed in case of ECG or clinical abnormalities.*

As described in Section 9:

- Blood [redacted] PK assays.

  [redacted]

As necessary:

- Electrocardiogram (ECG).

  ECG traces must be checked by an attending physician, consultant or specialist registrar, at the time of generation. A comment confirming normal/abnormal must be added along with a signature and date on the ECG to confirm review. Abnormal ECGs must be reviewed by a Cardiologist prior to dosing.

- Cardiac Troponin T or I.

[redacted]

8.6 Evaluations at 'Off-Study' visit

Evaluations at the 'Off-Study' visit should be performed 28 days ±7 days after the last dose of AZD3965. The following investigations must be done:

- Symptom-directed physical examination including WHO performance status, temperature, pulse rate, seated BP, and bodyweight.
- Haematology tests: detailed in Section 8.1.5.
- Biochemistry tests: detailed in Section 8.1.5.
- Urinalysis: detailed in Section 8.1.5.
- Chest X-ray (unless otherwise indicated by the patient's condition or, in the case of chest X-ray, to monitor the tumour status). A CXR may not be required if a CT/MRI scan has included the thorax.
- Assessment of tumour disease (radiological, clinical – if applicable, and tumour markers), unless assessment has been performed within the previous four weeks (28 days).
- Assessment of AEs (also see Section 10).
- Assessment of concomitant treatments.
- ECG (include measurement of QTc and verified manually (QTcF correction)).

  ECG traces must be checked by an attending physician, consultant or specialist registrar, at the time of generation. A comment confirming normal/abnormal must be added along with a signature and date on the ECG to confirm review. Abnormal ECGs should be reviewed by a Cardiologist.
- Cardiac Troponin T or I.
- Ophthalmic test: Best corrected visual acuity.
- Pattern and full-field ERG (or equivalent ERG assessment as previously agreed with the CDD) at the discretion of the ophthalmologist.

[redacted]

8.7 Follow-up

If any AEs and SAEs are considered to have a highly probable, probable or possible causal relationship to AZD3965, and are still present 28 days after the last administration of AZD3965 or occur in the 28 days post AZD3965 administration; then the patient will be followed up monthly afterwards until resolution, to baseline or stabilisation of these events, unless the patient starts another anti-tumour treatment.

8.8 Schedule of events for Part 2 (Cycles 1-12) of the study

Observation/Investigation	Pre-screening	Baseline/Pre-study			Standard Evaluations for each cycle (28 days)				Off study	Follow-up
	6 months prior to first dose	Day -28 to -1	Day -14 to -1	Day -7 to -1	Day 1	Day 8	Day 15	Day 22	28 +/-7 days after last dose of IMP	monthly **(p)**
AZD3965 administration					**Continuous daily dosing**					
Written informed consent	X	X								
Demographics		X								
Medical history		X								
Adverse event evaluation		From date of informed consent			Continually review				X	X
Concomitant treatments		From date of informed consent			Continually review				X	
Radiological (e.g. CT, PET/CT, MRI) disease assessment		X **(h)**			At the end of every 2 cycles				X **(o)**	
Available tumour sample for IHC profiling and DNA profiling **(a)**	X									
[redacted]		[redacted]			[redacted]					
Urinalysis				X	X **(r)**	X **(n)**	X	X **(n)**	X	
Pregnancy test (serum/ urine HCG) **(d)**			X							
Echocardiogram (ECHO)			X		Repeat if clinically indicated					
Ophthalmic test			X		X **(e)**				X	
Electro-retinography (ERG)			X		Every 28 days or as required **(m)**				X **(m)**	
Eye questionnaire						X **(l)**	X **(l)**	X **(l)**		
Haematology and biochemistry **(c)**				X **(s)**	X **(s)**	X **(n)**	X	X **(n)**	X	
Coagulation (PT)				X						
Cardiac troponin T or I				X	X **(r) (j)**	X **(n)**	X	X **(n)**	X	
Clinical disease assessment, tumour serum markers (if applicable)				X	At the end of every 2 cycles				X **(q)**	
Symptom-directed physical examination				X **(f)**	X **(r)**	X **(l)**	X **(l)**	X **(l)**	X	
WHO performance status				X	X **(r)**				X	
Weight				X	X **(r)**				X	
Temperature				X	X **(r)**	X **(n)**	X	X **(n)**	X	
Blood pressure (seated) and pulse rate				X	X **(r)**	X **(n)**	X	X **(n)**	X	
Electrocardiogram (ECG) **(g)**				X	X **(t)**	X **(n)**	X	X **(n)**	X	
Chest X-ray				X **(h)**	Repeat if clinically indicated				X	
[redacted]				[redacted]	[redacted]					

Observation/Investigation	Pre-screening	Baseline/Pre-study			Standard Evaluations for each cycle (28 days)				Off study	Follow-up
	6 months prior to first dose	Day -28 to -1	Day -14 to -1	Day -7 to -1	Day 1	Day 8	Day 15	Day 22	28 +/-7 days after last dose of IMP	monthly **(p)**
[redacted]					[redacted]					
[redacted]					[redacted]					
[redacted]				[redacted]	[redacted]					
Blood for pharmacokinetic assays **(k)**					Cycle 1 Day 1					
[redacted]				[redacted]	[redacted]				[redacted]	

(a) Ensure available biopsy material is available to confirm patient eligibility. Historical tumour biopsy sample can be obtained within 6 months prior to first dose. Fresh (new) screening tumour biopsy must be performed/obtained within 8 weeks prior to first dose.

[redacted]

(c) In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia a full blood count must be performed at least on Day 5 after the onset of the event to determine if a dose limiting toxicity has occurred. Continue close monitoring until resolution to Grade 3 or less.

(d) If the patient is a woman of child bearing potential.

(e) Ophthalmic test: best corrected visual acuity. **Not required on Cycle 1 Day 1.**

(f) Full physical examination before treatment start

(g) ECG: including QTc measurement and verified manually (QTcF correction)

(h) If baseline CT/MRI scan included the thorax, a chest X-ray may not be necessary provided all windows are presented for review

(i) Accurate blood glucose measurement to be done immediately prior to [redacted]

(j) Cardiac Troponin T or I to be performed at 24 +/-2 hours post first dose and repeated at 48 ±2 hours post-dose. **If result is clinically significant, ECG to be performed including QTc measurement and verified manually (QTcF correction)**

([redacted]

(l) During Cycle 1 only

(m) Pattern and full-field electro-retinography (ERG) (light and dark adapted) to be performed at the end of Cycle 1 +/-3 days and then repeated every 28 +/-3 days (or earlier if weekly Ophthalmic test suggest toxicity) if the patient reports symptoms of eye toxicity/changes in their vision. ERGs can be stopped after the end of Cycle 1 if no symptoms are reported and the Ophthalmologist agrees no further testing is required. **Off-study ERG to be performed at the discretion of the ophthalmologist only.**

(n) During Cycles 1 and 2 only

(o) Unless assessment has been performed within the previous four weeks (28 days)

(p) Monthly follow-up required ONLY for those AEs and SAEs considered DRUG-RELATED (highly probably, probably or possibly) and which are ongoing at the Off-Study visit. Monthly follow-up should continue until resolution, return to baseline, stabilisation or patient starts another anti-cancer treatment.

[redacted]

(r) Not required on Cycle 1 Day 1

(s) Bloods to include lactate and bicarbonate during screening and Cycle 1 Day 1 (post first dose)

(t) Hourly ECG assessments not required on Cycle 1 Day 1. ECG assessment **is required** 24 hours after first dose of AZD3965, including QTc measurement and verified manually (QTcF correction)

(u) Following the Cycle 1 Day 1 scan, [redacted]

8.8.1 Schedule of events for Part 2, Cycle 13 onwards

Observation/Investigation	Standard Evaluations for each cycle (28 days)	Off study	Follow-up
	Day 1	28 +/-7 days after last dose of IMP	Monthly **(a)**
AZD3965 administration	**Continuous daily dosing**		
Available tumour sample for IHC profiling and DNA profiling **(b)**			
Adverse event evaluation	Continually review	X	X
Concomitant treatments	Continually review	X	
Urinalysis	X **(h)**	X	
Haematology and biochemistry	X **(h)**	X	
Symptom-directed physical examination	X **(h)**	X	
WHO performance status	X **(h)**	X	
Weight	X **(h)**	X	
Temperature	X **(h)**	X	
Blood pressure (seated) and pulse rate	X **(h)**	X	
Radiological (e.g. CT, PET/CT, MRI) disease assessment, clinical disease assessment, tumour serum markers (if applicable)	At the start of every 3 cycles	X **(f)**	
Ophthalmic test **(d)**	At the start of every 3 cycles	X	
Electro-retinography (ERG)	At the start of every 3 cycles	X	
Echocardiogram (ECHO)	At the start of every 6 cycles / as required		
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		
Cardiac troponin T or I	As required **(e)**	X	
Electrocardiogram (ECG) **(c)**	As required **(e)**	X	
Chest X-ray	As required **(e)**	X	

(a) Monthly follow-up required ONLY for those AEs and SAEs considered DRUG-RELATED (highly probably, probably or possibly) and which are ongoing at the Off-Study visit. Monthly follow-up should continue until resolution, return to baseline, stabilisation or patient starts another anti-cancer treatment.
(b) Sample already obtained (pre-screening).
(c) ECG: including QTc measurement and verified manually (QTcF correction).
(d) Ophthalmic test: best corrected visual acuity.
(e) May be repeated if clinically indicated or deemed necessary by the Investigator.
(f) Unless assessment has been performed within the previous four weeks (28 days).
(g) Unless otherwise indicated by the patient's condition or to monitor the tumour status). A CXR may not be required if a CT/MRI scan has included the thorax.
(h) May also be performed at Day 15 if necessary.

9 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

9.1 Part 1 Sampling summary

RECRUITMENT TO PART 1 OF THE STUDY IS NOW CLOSED

For details of sampling in Part 1 of this clinical trial, please refer to Protocol V 12.0 dated 22Aug2018 which still includes the details from this part of the trial.

9.2 Part 2 Sampling summary

Name of assay	Purpose of assay	Type of sample	Approximate volume per patient (a)	Timings (see exact timings later in this section)
Primary endpoint (Part 1 only)				
Secondary endpoints				
PK	Determination of plasma PK	Plasma	15 mL	Cycle 1 Day 1, pre- and post-dose
[redacted]				

(a) The total amount of blood taken per patient will be approximately 195 mL and a maximum of 215 mL (Cycles 1-12). From Cycle 13-24, approximately 100 mL will be drawn.
(b) If treatment continues after 24 cycles, approximately 80 mL of blood will be drawn over each 12 cycles.

Please refer to the study laboratory manual for current details of sample volumes, sample handling and storage instructions and shipment details.

9.3 Primary assay – Pharmacodynamic - Lactate accumulation in PBMCs (Part 1 only)

Part 1 only

For details of assays performed in Part 1 of this clinical trial, please refer to Protocol V 12.0 dated 22Aug2018 which still includes the details from this part of the trial.

9.4 Secondary assays

9.4.1 Secondary Assays - AZD3965 Pharmacokinetics

AZD3965 will be measured in whole blood according to agreed SOPs and validated methods.

A sample of blood will be collected into EDTA vacutainers from patients at the following time-points:

Part 1:

For details of assays performed in Part 1 of this clinical trial, please refer to Protocol V 12.0 dated 22Aug2018 which still includes the details from this part of the trial.

Part 2:

- Pre-treatment (pre-dose on Cycle 1 Day 1) and after the first dose on Cycle 1 Day 1 at 4 and 6 hours post dose and at 24 hours post-morning dose (prior to next dose). For patients receiving AZD3965 on a twice daily dosing schedule, an extra sample will be required at 12 hours post the morning dose (prior administration of their second dose of the day).

For Part 2 the approximate total volume of blood withdrawn from each patient for PK analysis will be 15mL depending on the dosing schedule for the patient. The total amount of blood taken per patient will be approximately 195 mL and a maximum of 215 mL (Cycles 1-12). From Cycle 13-24, approximately 100 mL will be drawn. If treatment continues after 24 cycles, approximately 80 mL of blood will be drawn over each 12 cycles.

Timing tolerances of ± the following are acceptable.

- 15 to 30 minutes: 5 minutes
- 1 to 2 hours: 10 minutes
- 4 to 6 hours: 1 hour
- 12 to 48 hours: 2 hours

These time-points may be revised as more data on AZD3965 PK becomes available, but the overall number of sample timepoints will not be increased.

Please refer to the Study Laboratory Manual for handling, storage and shipment of samples.

9.4.2 Secondary assays – Pharmacodynamics - Cell Death Biomarkers (M65, M30, nDNA) (Part 1 only)

Part 1 only

For details of assays performed in Part 1 of this clinical trial, please refer to Protocol V 12.0 dated 22Aug2018 which still includes the details from this part of the trial.

9.5 Tertiary/research assays

[redacted]

[redacted]

[redacted]

[redacted]

9.6 Storage and Shipment of Samples

Blood and tumour samples will be taken at the local participating clinical site for either local storage (until the Sponsor confirms shipping requirements and receiving laboratory) or will be shipped to a central analysing laboratory. The Sponsor will define the local storage requirements prior to shipment or will coordinate the shipment of the sample to the central laboratory. Thereafter, storage of remaining samples will be as per Sponsor agreements with the relevant laboratories.

10 ASSESSMENT OF SAFETY

10.1 Investigator responsibilities

The investigator is responsible for monitoring the safety of patients who have enrolled in the study and for accurately documenting and reporting information as described in the following sections.

10.1.1 Medical cover

The Chief/Principal Investigator (CI/PI) is also responsible for ensuring patients have access to 24 hour advice and/or care. Patients will be provided with the necessary contact numbers for both normal working and out of hours care. A copy of the protocol must be made available out of hours to ward staff and clinicians on call so that the appropriate advice may be given to the patient, the patient's relative or other care giver (for example General Practitioner). The CI/PI must ensure that should the on call clinician or ward staff require more advice than is in this protocol, that they have access to the Investigator or delegated members of the investigator's team who can answer any questions.

10.2 Adverse event definitions

10.2.1 Adverse event

An AE is any untoward, undesired or unplanned occurrence in a patient administered an IMP, a comparator product or an approved drug.

An AE can be a sign, symptom, disease, and/or laboratory or physiological observation that may or may not be related to the IMP or comparator.

An AE includes but is not limited to those in the following list.

- A clinically significant worsening of a pre-existing condition. This includes conditions that may resolve completely and then become abnormal again.
- AEs occurring from an overdose of an IMP, whether accidental or intentional.
- AEs occurring from lack of efficacy of an IMP, for example, if the Investigator suspects that a drug batch is not efficacious or if the Investigator suspects that the IMP has contributed to disease progression.

10.2.2 Serious adverse events

A serious adverse event (SAE) is any AE, regardless of dose, causality or expectedness, that:

- results in death;
- is life-threatening *;
- requires in-patient hospitalisation *or* prolongs existing in-patient hospitalisation (some hospitalisations are exempt from SAE reporting – e.g. hospital admissions planned prior to the patient entering the trial; overnight stays for planned procedures such as blood transfusions (Section 10.4.1);
- results in persistent or significant incapacity or disability;
- is a congenital anomaly or birth defect;
- is any other medically important event**.

* A life-threatening event is defined as an event when the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.

** A medically important event is defined as any event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Trial-specific medically important events

Any ophthalmic and/or cardiac event that meets DLT criteria is considered a medically important event in this trial. Therefore, all ophthalmic and cardiac DLTs must be reported as SAEs.

For fatal SAEs, wherever possible report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term. When available the autopsy report will be provided to the Sponsor.

If during the course of the study, other medically important events are identified and there is a requirement to report specific events outside of the standard criteria, this will be communicated to site and the protocol will be updated to reflect this.

Any dose limiting toxicity (DLT) must be reported to the CDD Clinical Study Manager (CSM) and CRA within 24 hours of site staff becoming aware of the DLT. The CDD Pharmacovigilance Department must be copied into any initial email notification.

Other reportable events that must be treated as SAEs are listed below.

- Pregnancy exposure to the IMP. Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within six months of the last IMP administration, must be reported to the Pharmacovigilance Department in the same timelines as an SAE. These should be reported even if the patient is withdrawn from the trial.
- Overdose with or without an AE *(any dose above that specified in the protocol, not necessarily intentional)*.
- Inadvertent or accidental exposure to an IMP with or without an AE, including for example, spillage of the IMP that contaminates staff.
- Any AE that could be related to the protocol procedures, and which could modify the conduct of the trial.

10.2.3 Suspected, unexpected, serious adverse reactions

A SUSAR is a suspected, unexpected, serious adverse reaction. All AEs and SAEs will be assessed by CDD for seriousness, causality and expectedness. The Pharmacovigilance department will expedite all SUSARs to the relevant Competent Authority/Authorities and the relevant Ethics Committee(s) within the timelines specified in legislation (SI 2004/1031 as amended).

10.2.4 Determining adverse event causality

The relationship of an AE to the IMP is determined as follows.

Highly probable • Starts within a time related to the IMP administration and • No obvious alternative medical explanation.
Probable • Starts within a time related to the IMP administration and • Cannot be reasonably explained by known characteristics of the patient's clinical state.
Possible • Starts within a time related to the IMP administration and • A causal relationship between the IMP and the AE is at least a reasonable possibility.
Unlikely • The time association or the patient's clinical state is such that the trial drug is not likely to have had an association with the observed effect.
Not related • The AE is definitely not associated with the IMP administered.

Note: Drug-related refers to events assessed as possible, probable or highly probable.

The Investigator must endeavour to obtain sufficient information to determine the causality of the AE (i.e. IMP, other illness, progressive malignancy etc) and must provide his/her opinion of the causal relationship between each AE and IMP. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

The following guidance should be taken in to account when assessing the causality of an AE:

- Previous experience with the IMP and whether the AE is known to have occurred with the IMP.
- Alternative explanations for the AE such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding effects.
- Timing of the events between administration of the IMP and the AE.
- IMP blood levels and evidence, if any, of overdose.
- De-challenge, that is, if the IMP was discontinued or the dosage reduced, what happened to the adverse reaction?
- Re-challenge, that is, what happened if the IMP was restarted after the AE had resolved?

10.2.5 Expectedness

Assessment of expectedness for AZD3965 will be made by the Pharmacovigilance Department against the current version of the Investigator's Brochure.

10.3 Collecting of safety information

10.3.1 Pre-Screening

Following pre-screening informed consent, any SAEs that are considered by the Investigator to be related to the pre-screening biopsy must be reported to the Pharmacovigilance Department, CDD.

10.3.2 Screening failures

For patients who fail screening, SAEs must be reported to the Pharmacovigilance Department, CDD from the date of consent until the date the patient is confirmed as ineligible.

10.3.3 Eligible patients

For eligible patients, SAE and AE collection and monitoring commences from the time the patient gives their written consent to participate in the trial and continues for 28 days after the last administration of AZD3965 (IMP).

10.3.4 Follow-up of AEs and SAEs

Follow-up of non-serious AEs with a causality of possible, probable or highly probable will continue until the events resolve, stabilise or the patient starts another anti-cancer therapy.

Any SAEs or AEs considered to be related (possibly, probably or highly probably) to AZD3965 occurring either 28 days post AZD3965 administration or are still present 28 days after the last administration of AZD3965, should be reported to the CDD Pharmacovigilance department as per the timelines stated in section 10.4.

The Pharmacovigilance Department will make requests for further information on SAEs to the trial site at regular intervals. Requested follow-up information should be reported to the Pharmacovigilance Department in a timely manner and as soon as possible after receipt of the follow-up request. For fatal or life-threatening cases, follow-up information must be reported to the Pharmacovigilance Department as soon as possible.

10.3.5 Other safety information of interest

We will also collect information on the following situations, whether they are associated with an AE or not:

- Abuse or misuse

Any occurrences of these should be reported in the same manner as SAEs (Section 10.4).

10.4 Reporting of SAEs to the Pharmacovigilance Department, CDD

All SAEs, regardless of causality, must be reported to the Pharmacovigilance Department in an expedited manner.

SAEs should be documented on an SAE report form, using the completion guidelines provided.

The SAE report form should be <u>e-mailed</u> to Pharmacovigilance Department within 24 hours of site staff becoming aware of the SAE.

[redacted]

Each episode of an SAE must be recorded on a separate SAE report form. The NCI CTCAE Version 4.02 must be used to grade each SAE, and the worst grade recorded. If new or amended information on a previously reported SAE becomes available, the Investigator should report this to the Pharmacovigilance department on a new SAE report form.

If the SAE has not been reported within the specified timeframes, a reason for lateness must be added on the form when sending the SAE report form to the Pharmacovigilance department.

Should the Investigator become aware of any drug-related SAEs after the patient goes ‘off study’, these must also be reported to the Pharmacovigilance department within the specified timelines above.

10.4.1 Events exempt from being reported as SAEs to the Pharmacovigilance department

Events specified in this section do not require reporting as SAEs in this trial, unless hospitalisation is prolonged for any reason and then an SAE form must be completed. The events must still be recorded in the appropriate section of the eCRF.

Elective admissions – Elective admissions to hospital for procedures which were planned prior to entering the trial are not SAEs. Hospitalisation for administration of the IMP according to the trial protocol is also exempt from being reported as an SAE, unless the patient experiences an event during the admission which would normally qualify as an SAE.

Death due to disease progression – Cases of death due to disease progression do not require SAE reporting, unless considered related to the IMP.

10.5 Recording of adverse events and serious adverse events in eCRFs

All AEs, including SAEs, must be recorded in the eCRF for eligible patients. All concomitant medications, including herbal medications and supplements must be recorded. Any therapy used to treat the event must be recorded. The eCRF will be reconciled with the safety database during and at the end of the trial. Therefore, the sites should ensure the data entered on the SAE report form and the data entered into the eCRF are consistent. The CDD Medical Advisor and the Investigator(s) will regularly review the safety data from both the safety and the clinical database.

10.6 Urgent safety measures

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) in order to protect the patient of a clinical trial against any immediate hazard to their health or safety. This includes procedures taken to protect patients from pandemics or infections that pose serious risk to human health.

USMs may be taken without prior authorisation from the competent authority.

The Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC) must be notified within three days of such measures being taken.

Should the site initiate a USM, the Investigator must inform the Sponsor immediately either by:

- [redacted]
- [redacted]

The notification must include:

- the date of the USM;
- who took the decision; and
- why action was taken.

The Sponsor will then notify the MHRA and the REC within three calendar days of USM initiation.

10.7 Pregnancy

Female patients who become pregnant from the time of informed consent being signed to off-study, must be withdrawn from study treatment immediately.

The Investigator must make every effort to try and ensure that a clinical trial patient or a partner of a clinical trial patient does not become pregnant during the trial or for six months afterwards. This should be done as part of the consent process by explaining clearly to the patient (and parent/legal guardian, if appropriate) the potential dangers of becoming pregnant and also providing each patient (and parent/legal guardian, if appropriate) with information about appropriate medically approved contraception. Two forms of medically approved contraception should be used, such as:

- Oral contraceptives and condom; (oral, injected or implanted hormonal contraceptives should be used for four weeks before the patient joins the study)
- intra-uterine device (IUD) and condom;
- diaphragms with spermicidal gel and condom.

Contraception should be effective before the patient is enrolled on the trial, throughout the trial and for six months after completing the trial.

Alternatively the patient may agree to sexual abstinence, effective from the first administration of *IMP*, throughout the trial and for *six* months afterwards. Abstinence is only considered to be an acceptable method of contraception when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

It should be explained to a male patient (and parent/legal guardian, if appropriate) that if his partner is pregnant or breast-feeding when he is enrolled on the trial, the patient should use barrier method contraception (condom plus spermicidal gel) to prevent the unborn baby or the baby being exposed to AZD3965.

However, if a patient or a partner of a patient does become pregnant, the reporting procedures below must be followed.

Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within six months of last IMP administration must be reported to the Pharmacovigilance Department within 24 hours of the site staff becoming aware of it using a Pregnancy Report Form (provided in the ITF). It is the Investigator's responsibility to obtain consent for follow-up from the patient or patient's partner. In addition, the Investigator must be made aware of the need to obtain contact details for the patient's partner's General Practitioner. The Pharmacovigilance Department will follow-up all pregnancies for the pregnancy outcome via the Investigator, using a Pregnancy Report Form.

The Investigator must ensure that all patients are aware at the start of a clinical trial of the importance of reporting all pregnancies (in themselves and their partners) that occur whilst being treated with the IMP and occurring up to six months after the last IMP administration. The Investigator should offer counselling to the patient and/or the partner, and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient or partner should continue until the conclusion of the pregnancy, if the patient or patient's partner has consented to this. Monitoring of the baby should continue until 12 months after birth, if the patient or patient's partner has consented to this.

11 ASSESSMENT OF EFFICACY

11.1 Measurement of disease

Disease must be measured according to the RECIST criteria v1.1 given in Appendix 2A or to the International Working Group (IWG) criteria for lymphoma (Cheson, Pfistner *et al*, 2014) in Appendix 2B.

11.2 Timing and type of tumour assessments

A thorough clinical and radiological evaluation of malignancy, as judged appropriate by the Investigator, and in line with the protocol, must be performed before starting the investigational medicinal product (IMP). The same methods that detect evaluable lesions at baseline must be used to follow these lesions throughout the trial. To ensure compatibility, the radiological assessments used to assess response must be performed using identical techniques. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment.

All radiological assessments must be performed within four weeks before starting treatment. The interval between the last anti-cancer therapy and these measurements must be at least four weeks (28 days). All clinical measurements to assess response must be done within **one** week before the patient starting treatment.

All complete (CR) and partial responses (PR) must be confirmed by two consecutive observations not less than four weeks apart.

Copies of the scans must be available for external independent review if requested by the CDD.

11.2.1 Baseline evaluations

These must include radiological measurements and as indicated chest computerised tomography (CT) scan, abdominal CT scan, magnetic resonance imaging (MRI), [^{18}F]FDG-PET scan, bone scan and/or clinical measurements as appropriate. All areas of disease present must be documented (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded clearly on the scan reports. Any non-measurable lesions must be stated as being present. For clinical measurements, documentation by colour photography including a ruler to estimate the size of the lesion is strongly recommended, as this aids external independent review of responses (see Appendix 2A and 2B).

If a lesion is FDG avid it can be considered to contain tumour and be measured. Any mass, of any size that is FDG negative by PET, cannot be considered to be disease. A positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology, without a specific standardized uptake value cut-off. Other causes of false-positive scans should be ruled out. Exceptions include mild and diffusely increased FDG uptake at the site of moderate or large-sized masses with an intensity that is lower than or equal to the mediastinal blood pool, hepatic or splenic nodules 1.5 cm with FDG uptake lower than the surrounding liver/spleen uptake and diffusely increased bone marrow uptake within weeks after treatment. Specific criteria for lung nodules based on lesion size have been developed. (Cheson, Pfistner *et al*, 2014).

11.2.2 Evaluations during and at Off-study visit

Tumour assessments must be repeated every 2 cycles/8 weeks (Cycles 1-12) and every 3 cycles/ 12 weeks (Cycle 13 onwards) or more frequently, when clinically indicated. All lesions measured at baseline must be measured at every subsequent disease assessment and recorded clearly on the scan reports. All non-measurable lesions noted at baseline must be noted on the scan report as present or absent.

All patients, who are removed from the trial for reasons other than progressive disease, must be re-evaluated at the time of treatment discontinuation, unless a tumour assessment was performed within the previous four weeks.

It is the responsibility of the Principal Investigator to ensure that the radiologists are aware of the requirement to follow-up and measure every target lesion mentioned at baseline and comment on the non-target lesions in accordance with RECIST criteria or the IWG criteria for lymphoma (Appendix 2A and 2B).

11.3 Tumour response

All patients who meet the eligibility criteria and receive at least 75 % of their first cycle of trial medication and have a baseline assessment of disease will be evaluable for response. To be assigned a status of CR or PR, changes in tumour measurements must be confirmed by repeat measurements performed no less than four weeks after the response criteria are met. To be assigned a status of stable disease (SD), follow-up measurements must have met the SD criteria at least once and at least six weeks after the initial dose of the investigational medicinal product (IMP) AZD3965 is given.

Should rapid tumour progression occur before the completion of 4 weeks, the patient will be classified as having early progression (EP).

Tumour response should be classified as “not evaluable” (NE), only when it is not possible to classify it under another response category, for example, when baseline and/or follow-up assessment is not performed or not performed appropriately.

Expert reviewers appointed by CDD may undertake an independent review of all the Investigator’s assessed objective responses (CR and PR). The expert reviewers will include at least one specialist who is not an Investigator in the trial. In case of disagreement between the Investigator’s and the expert

reviewers' assessment, discussion will take place between the two parties in order to reach a consensus. However, if it is not forthcoming, the assessment of the expert reviewers will be retained in the clinical study report. The eCRF will reflect the Investigator's opinion.

11.3.1 Recording of response in the eCRF

The applicable overall response category for each visit that includes disease assessment must be recorded in the eCRF, even though the criteria for determination of CR or PR by the protocol must be confirmed after two consecutive observations, no less than four weeks apart.

11.3.2 Other definitions of outcome

Toxic death: Any death to which drug toxicity is thought to have a major contribution.

Early death: Death during the first cycle/28 days of treatment.

12 PATIENT WITHDRAWAL BEFORE COMPLETION OF TREATMENT SCHEDULE

The Investigator must make every reasonable effort to keep each patient on trial for the whole duration of the trial (i.e. until the Off-Study visit 28±7 days after last dose of AZD3965). However, if the Investigator removes a patient from the trial or if the patient declines further participation, final 'Off-Study' assessments should be performed before any therapeutic intervention. All the results of the evaluations and observations, together with a description of the reasons for withdrawal from the trial, must be recorded in the medical records and in the eCRF.

Patients who are removed from the trial due to adverse events (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the eCRF and on the serious adverse event (SAE) report form where necessary.

The following are justifiable reasons for the Investigator to withdraw a patient from trial.

- AE/SAE
- Withdrawal of consent
- Serious violation of the trial protocol (including persistent patient attendance failure and persistent non-compliance)
- Sponsor's decision to terminate the trial
- Withdrawal by the Investigator for clinical reasons not related to the IMP (AZD3965)
- Evidence of disease progression
- Pregnancy (for female patients during the trial)

For the purposes of this trial a patient who completes six or more treatment cycles is considered to have completed the trial.

13 DEFINING THE END OF TRIAL

The 'end of trial' is defined as the date when the last patient has completed the 'Off-Study' visit or the final follow-up visit (whichever is the later).

It is the responsibility of the CDD to inform the Medicines and Healthcare products Regulations Agency (MHRA) and the Research Ethics Committee (REC) within 90 days of the 'end of the trial' that the trial has closed.

In cases of early termination of the trial (for example, due to toxicity) or a temporary halt by the CDD, the CDD will notify the MHRA and the REC within 15 days of the decision and a detailed, written explanation for the termination/halt will be given.

The entire trial will be stopped when:

- The IMP is considered too toxic to continue treatment before the required number of patients being recruited.
- The stated number of patients to be recruited is reached.
- The stated objectives of the trial are achieved.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the trial, CDD and the Investigators must ensure that adequate consideration is given to the protection of the patient's interest.

14 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

The final analysis will be conducted after one of the following conditions is met.

- The trial is terminated early (for example, due to toxicity).
- All patients have had the opportunity to receive treatment and have completed their Off-study visit (i.e. 28±7 days after the last dose of AZD3965) or final follow up.

Once one of the conditions is met, a data cut-off date will be established. All patient visits occurring on or before this date will be analysed and summarised in the final clinical study report.

A clinical data cut-off date will be established to allow for primary analysis Clinical Study Report (CSR) reporting once all recruited patients have received up to 12 cycles of AZD3965. The primary analysis CSR will include data from all treated patient visits/assessments up to and including the clinical data cut-off date, [redacted]

Any patients who continue to receive AZD-3965 in the absence of disease progression or unacceptable toxicity after the clinical data cut-off date will be included in an addendum to the final CSR. [redacted]

14.1 Presentation of data

Data will be presented in a descriptive fashion. Variables will be analysed to determine whether the criteria for the trial conduct are met. This will include a description of patients who did not meet all the eligibility criteria, an assessment of protocol violations, IMP accountability and other data that impact on the general conduct of the trial.

Baseline characteristics will be summarised for all enrolled patients. Patients who died or withdrew before treatment started or did not complete the required safety observations will be described and evaluated separately.

Treatment administration will be described for all cycles. Dose administration, dose modifications or delays and the duration of therapy will be described.

14.2 Safety

Safety data will be collected from the date of written consent. Safety variables will be summarised by descriptive statistics. Laboratory variables will be described using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02.

Adverse events will be reported for each dose level and presented as tables of frequency of AEs by body system and by worse severity grade observed. Tables should indicate related and unrelated events. Laboratory data will be presented by dose level at each observation time. Values outside normal limits will be identified in the listings.

14.3 Pharmacokinetics

Plasma will be separated and analysed to determine the concentrations of AZD3965 using a previously developed LCMS method. Parameters to be calculated will include: area under the plasma concentration-time curve (AUC_{0-t}), maximum concentration achieved (C_{max}), time to maximum concentration (T_{max}) and elimination half-life ($T_{1/2}$) for AZD3965.

At the end of the trial when all the data has been analysed, a full PK report will be produced for inclusion in the final clinical study report.

[redacted]

14.5 Anti-tumour activity

Documenting anti-tumour activity is a secondary objective of this trial. Patients must receive at least 75% of their first cycle of the trial medication to be evaluable for response. Objective responses, the best tumour response achieved by each patient while on trial and the time to progression will be presented in the data listings.

14.6 Exploratory work

[redacted]

15 ADMINISTRATION

This trial is conducted under a clinical trial authorisation (CTA) and approval from the Medicines and Healthcare products Regulations Agency (MHRA) and the relevant Research Ethics Committee(s) will be obtained before the start of this trial. This trial is sponsored and monitored by the CRUK CDD. Applicable regulatory requirements are described in this section.

15.1 Protocol deviations and amendments

Do not deviate from the protocol unless approval has been obtained from the CDD.

Amendments to the protocol may only be made with the approval of the CDD. A protocol amendment may be subject to review by the assigned Ethics Committee, HRA and the MHRA. Written documentation of the Ethics Committee and HRA (and if appropriate the MHRA) 'favourable opinion' (i.e. approval) must be received before the amendment can be implemented and incorporated into the protocol if necessary.

15.2 Completion of the electronic case report form (eCRF)

Electronic CRFs approved by the CDD will be used to collect the data. The Investigator is responsible for ensuring the accuracy, completeness, clarity and timeliness of the data reported in the eCRFs.

Only the Investigator and those personnel who have signed the Delegation Log provided by the CDD and have been authorised by the Investigator should enter or change data in the eCRFs. Authorised

users will be included on a User Management Tool Form in order to be provided access to the eCRF. All protocol required investigations must be reported in the eCRF. The Investigators must retain all original reports, traces and images from these investigations for future reference.

Data will be entered directly into electronic screens by authorised site personnel. Amendments to eCRF data will be made directly to the system and the system audit trail will retain details of the original value(s), who made the change, a date and time, and a reason for the change.

Once an eCRF form has been entered by the site personnel, the data are cleaned using manual and automated checks. Queries will be issued electronically to the site. Authorised personnel must answer the queries by making relevant amendments to data or providing a response. Answered queries will be closed or reissued as appropriate.

Once the patient is 'off study' and the eCRF has been fully completed, the Investigator must provide an electronic signature to authorise the complete subject casebook.

At the end of the trial all eCRFs are retained and archived by the CDD and a PDF copy provided to the Investigator who is responsible for archiving at site.

15.3 Trial performance and monitoring

Before the trial can be initiated, the prerequisites for conducting the trial must be clarified and the organisational preparations made with the trial centre. CDD must be informed immediately of any change in the personnel involved in the conduct of the trial.

During the trial the CDD Clinical Research Associate (CRA) is responsible for monitoring data quality in accordance with CDD's standard operating procedures (SOPs). Before the trial start, the Investigator will be advised of the anticipated frequency of the monitoring visits. The Investigator will receive reasonable notification before each monitoring visit.

It is the responsibility of the CRA to:

- review trial records and compare them with source documents;
- check pharmacokinetic and pharmacodynamic samples and storage;
- discuss the conduct of the trial and the emerging problems with the Investigator;
- check that the drug storage, dispensing and retrieval are reliable and appropriate; and
- verify that the available facilities remain acceptable.

All the unused drug supplied must be returned to the supplier, or if authorised by Cancer Research UK properly destroyed at the Investigator site by an authorised person who will provide signed confirmation.

It is the responsibility of the Sponsor to inform the Main REC within 90 days of the 'end of the trial' that the trial has closed (see definition in Section 13).

15.4 Source document verification

Unless agreed in writing, all data collected in the eCRF must be verifiable by the source data. Therefore it is the Investigator's responsibility to ensure that both he/she and his/her study team records all relevant data in the medical records. The Investigator must allow the CRA direct access to relevant source documentation for verification of data entered into the eCRF, taking into account data protection regulations. Entries in the eCRF will be compared with patients' medical records and the verification will be recorded in the eCRF, documented on the source data verification (SDV) form and the monitoring report.

Some source data may exist only electronically and be entered, or loaded directly into the eCRF.

The patients' medical records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the CDD appointed to audit the trial, and by regulatory authorities. Details will remain confidential and patients' names will not be recorded outside the hospital.

15.5 Clinical study report (CSR)

All clinical data will be presented on final data listings. CDD will prepare a CSR (plus addendum if applicable) based on the final data listings. The report(s) will be submitted to the Investigator(s) for review and confirmation it accurately represents the data collected during the course of the trial. Summary results of the trial will be provided by the CDD to the MHRA and to the REC within one year of the 'End of Trial'.

Any patients who continue to receive AZD-3965 in the absence of disease progression or unacceptable toxicity after the clinical cut-off date will be included in an addendum to the final CSR.

15.6 Record retention

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable both the conduct of a clinical trial and the quality of the data produced to be evaluated and verified. These essential documents (as detailed in Chapter V of Volume 10 (Clinical Trials) of The Rules Governing Medicinal Products in the European Union based upon Section 8 of the ICH GCP Guidelines), including source documents such as scans, trial related documents and copies of the eCRFs, associated audit trail and SAE report forms, shall show whether the Investigator has complied with the principles and guidelines of Good Clinical Practice (GCP).

All essential documents required to be held by the Investigator must be stored in such a way that ensures that they are readily available, upon request, to the Regulatory Agency or Sponsor, for the minimum period required by national legislation or for longer if needed by CDD. Records must not be destroyed without prior written approval from CDD.

The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

15.7 Ethical considerations

Before starting the trial, the protocol, patient information sheet and consent form must go through the CDD's external review process, and be approved by the PSRB and the appropriate Ethics Committee.

It is the Chief/Principal Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The Chief/Principal Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented.

The Sponsor and Chief/Principal Investigator must ensure that the trial is carried out in accordance with the GCP principles and requirements of the UK Clinical Trials regulations (SI 2004/1031 and SI 2006/1928 as amended), the ICH GCP guidelines and the Declaration of Helsinki.

15.8 Indemnity

This trial is being carried out under the auspices of Cancer Research UK and therefore injury to a patient caused by the compounds under trial will not carry with it the right to seek compensation from the pharmaceutical industry. Cancer Research UK will provide patients with compensation for adverse side effects, in accordance with the principles set out in the Association of the British Pharmaceutical Industry (ABPI) guidelines on compensation for medicine-induced injury.

15.9 Publication policy and press releases

Results of this trial must be submitted for publication. The CDD must be involved in reviewing all drafts of the manuscripts, abstracts, press releases and any other publications. Manuscripts must be submitted to CDD at least 30 days in advance of being submitted for publication to allow time for CDD to schedule a review and resolve any outstanding issues. Abstracts and press releases must be submitted to CDD at least 14 days in advance of being released. Authors must acknowledge that the trial was sponsored by and performed with the support of CDD.

The contribution of CDD must be recognised by at least one member of staff being included as an author on the publication.

16 REFERENCES

Cheson, Pfistner et al (2007). Revised Response Criteria for Malignant Lymphoma. *J Clin Onc* **25** (5): 579-86.

Eisenhauer, E.A., P. Therasse, J. Boagaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, I. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij (2009). New Response Evaluation Criteria in solid tumours: Revised RECIST guidelines (version 1.1). *European Journal of Cancer* **45:** 228-247

Gerhart, D. Z., R. L. Leino and L. R. Drewes (1999). "Distribution of monocarboxylate transporters MCT1 and MCT2 in rat retina." *Neuroscience.* **92**(1): 367-375.

Koho, N. M., M. Raekallio, E. Kuusela, J. Vuolle and A. R. Poso (2008). Lactate transport in canine red blood cells. *Am J Vet Res.* **69**(8): 1091-1096.

Sonveaux, P., F. Vegran, T. Schroeder, M. C. Wergin, J. Verrax, Z. N. Rabbani, C. J. De Saedeleer, K. M. Kennedy, C. Diepart, B. F. Jordan, M. J. Kelley, B. Gallez, M. L. Wahl, O. Feron and M. W. Dewhirst (2008). "Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice." *J Clin Invest.* 118(12): 3930-3942.

Skolnik, J.M., Barrett, J.S., Jayaramen, B., Patel, D., Adamson, P.C. (2008). "Shortening the timeline of pediatric Phase I trials: The rolling six design." *J Clin Oncol* **26**: 190-195.

Yap, Y.G., Camm, A.J. (2003). Drug induced QT prolongation and torsades de pointes*. Heart.* **89***,* 1363-1372.

Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. **July 2007.** *EMEA/CHMP/SWP/28367/07*

Note for Guidance on Good Clinical Practice. ICH Topic E6. CSMP/ICH/135/95. EMEA, May 1996, updated September 1997 with post Step 4 errata included

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Official Journal of the European Communities L121/34-44*

Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial. **October 2005***. ENTR/F2/BL D(2003) CT 1 (Revision 2)*

Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use. **February 2006.** *ENTR/CT 2 (Revision 1)*

Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. **April 2006.** *ENTR/CT 3 (Revision 2)*

The **Medicines** for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 1031)
COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. *Official Journal of the European Union L 91/13*

The Medicines for Human use (Clinical Trials) Amendment Regulations 2006 (Statutory Instrument 2006/1928).

17 APPENDICES

17.1 APPENDIX 1: WHO PERFORMANCE SCALE

Activity Performance Description	Score
Fully active, able to carry out all normal activity without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work.	1
Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.	4

17.2 APPENDIX 2A: MEASUREMENT OF DISEASE IN SOLID TUMOURS

New response evaluation criteria in solid tumours (RECIST criteria): Revised RECIST guideline (version 1.1)

E.A. Eisenhauer *et al*. (2009) *European Journal of Cancer* **45:** 228-247

Note that this is an abridged version of the RECIST criteria. Please refer to the above article for detailed appendices and if in doubt.

1. Measurability of tumour at baseline

1.1 Definitions

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

1.1.1 Measurable

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10 mm calliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be P15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed (see Schwartz et al. in this Special Issue15). See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with P10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3. Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2. Specifications by methods of measurements

1.2.1. Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2. Method of assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions:
Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray:
Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. See Appendix II for more details.

CT, MRI:
CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in Appendix II.

Ultrasound:
Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix II). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy:
The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers:
Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer.

Cytology, histology:
These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. Tumour response evaluation

2.1 Assessment of overall tumour burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 1). In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

2.2. Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts *et al*.. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance

the next largest lesion which can be measured reproducibly should be selected. To illustrate this point see the example in Fig. 3 of Appendix II.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. As noted in Section 3 of the article, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of P15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement (See also the example in Fig. 4 in Appendix II). All other pathological nodes (those with short axis P10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non- pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

2.3. Response criteria

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

2.3.1. Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.3.2. Special notes on the assessment of target lesions

Lymph nodes.

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes

regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'.
While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment.
As noted in Appendix II, when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3. Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.3.4. Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease.
In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix II and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease.
This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. Some illustrative examples are shown in Figs. 5 and 6 in Appendix II. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.3.5. New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.4. Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement (see Section 4.6). Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

2.4.1. Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

2.4.2. Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3. Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required:

Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable. A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Table 1 – Time point response: patients with target (+/–non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD

Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD(a) NE
Not all evaluated	No	PD
Unequivocal PD	Yes or No	PD
Any	Yes	

CR = complete response, PD = progressive disease, and NE = inevaluable.
(a) 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Best response determination in trials where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

Table 3 – Best overall response when confirmation of CR and PR required

Overall response	Overall response	BEST overall response
First time point	Subsequent time point	
CR	CR	CR
CR	PR	SD, PD or PR(a)
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
(a) If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely

still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.4.4. Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2.5. Frequency of tumour re-evaluation

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised

comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

2.6. Confirmatory measurement/duration of response

2.6.1. Confirmation

In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2.6.2. Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3. Duration of stable disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

17.3 APPENDIX 2B: MEASUREMENT OF DISEASE IN LYMPHOMA

Below is an excerpt of text from Cheson, Fisher et al; JCO 2014, 32; 3059-3067

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None

Response and Site	PET-CT–Based Response	CT-Based Response
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with:
		LDi > 1.5 cm and
		Increase by ≥ 50% from PPD nadir and
		An increase in LDi or SDi from nadir
		0.5 cm for lesions ≤ 2 cm
		1.0 cm for lesions > 2 cm
		In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (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
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions		Regrowth of previously resolved lesions
		A new node > 1.5 cm in any axis

Response and Site	PET-CT–Based Response	CT-Based Response
	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	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

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; 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 under treatment). 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, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (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 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

17.4 APPENDIX 3: CONCURRENT MEDICATION WITH A KNOWN RISK OF QT PROLONGATION

The lists below were last revised on 15Feb2019, Source: https://crediblemeds.org/. As drugs are reviewed on an ongoing basis to assure that the available evidence supports their continued placement on this list, the list changes regularly. **Therefore, check the website at crediblemeds.org for the most up-to-date information.**

Drugs given in Category 1 below should be excluded.

Category 1:

Substantial evidence supports the conclusion that these drugs prolong the QT interval and have a risk of TdP when used as directed in labelling (advised by Scientific Advisory Board of the Arizona Centre for Education and research on therapeutics (AZCERT)).

Generic Name	Brand Names (Partial List)	Therapeutic Use	Risk Category
Aclarubicin	Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin	Cancer	1
Amiodarone	Cordarone, Pacerone, Nexterone	Abnormal heart rhythm	1
Anagrelide	Agrylin, Xagrid	Thrombocythemia	1
Arsenic trioxide	Trisenox	Cancer (leukemia)	1
Astemizole (Removed from Market)	Hismanal	Allergic rhinitis	1
Azithromycin	Zithromax, Zmax	Bacterial infection	1
Bepridil (Removed from Market)	Vascor	Angina Pectoris (heart pain)	1
Chloroquine	Aralen	Malaria	1
Chlorpromazine	Thorazine, Largactil, Megaphen	Schizophrenia, nausea, many others	1
Cilostazol	Pletal	Intermittent claudication	1
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Bacterial infection	1
Cisapride (Removed from Market)	Propulsid	Increase GI motility	1
Citalopram	Celexa, Cipramil	Depression	1
Clarithromycin	Biaxin, Prevpac	Bacterial infection	1
Cocaine	Cocaine	Anesthesia (topical)	1
Disopyramide	Norpace	Abnormal heart rhythm	1
Dofetilide	Tikosyn	Abnormal heart rhythm	1
Domperidone (Only on Non US Market)	Motilium, Motillium, Motinorm Costi, Nomit	Nausea, vomiting	1
Donepezil	Aricept	Dementia (Alzheimer's Disease)	1
Dronedarone	Multaq	Abnormal heart rhythm	1

Generic Name	Brand Names (Partial List)	Therapeutic Use	Risk Category
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Anesthesia (adjunct), nausea	1
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Bacterial infection, increase GI motility	1
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E (India), Exodus (Brazil), Esto (Israel), Seroplex, Elicea, Lexamil, Lexam, Entact (Greece), Losita (Bangladesh), Reposil (Chile), Animaxen (Colombia), Esitalo (Australia), Lexamil (South Africa)	Depression (major), anxiety disorders	1
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Abnormal heart rhythm	1
Fluconazole	Diflucan, Trican	Fungal infection	1
Gatifloxacin (Removed from Market)	Tequin	Bacterial infection	1
Grepafloxacin (Removed from Market)	Raxar	Bacterial infection	1
Halofantrine (Only on Non US Market)	Halfan	Malaria	1
Haloperidol	Haldol (US & UK), Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol (Germany), Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Schizophrenia, agitation	1
Ibogaine (Only on Non US Market)	None	Narcotic addiction, unproven	1
Ibutilide	Corvert	Abnormal heart rhythm	1
Levofloxacin	Levaquin, Tavanic	Bacterial infection	1
Levomepromazine (methotrimeprazine) (Only on Non US Market)	Nosinan, Nozinan, Levoprome	Schizophrenia	1
Levomethadyl acetate (Removed from Market)	Orlaam	Narcotic dependence	1
Levosulpiride (Only on Non US Market)	Lesuride, Levazeo, Enliva (with rabeprazole)	Schizophrenia	1
Mesoridazine (Removed from Market)	Serentil	Schizophrenia	1

Generic Name	Brand Names (Partial List)	Therapeutic Use	Risk Category
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Narcotic dependence, pain	1
Moxifloxacin	Avelox, Avalox, Avelon	Bacterial infection	1
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Nausea, vomiting	1
Oxaliplatin	Eloxatin	Cancer	1
Papaverine HCl (Intra-coronary)	none	Diagnostic adjunct	1
Pentamidine	Pentam	Fungal infection (Pneumocystis pneumonia)	1
Pimozide	Orap	Tourette's Disorder	1
Probucol (Removed from Market)	Lorelco	Hypercholesterolemia	1
Procainamide	Pronestyl, Procan	Abnormal heart rhythm	1
Propofol	Diprivan, Propoven	Anesthesia	1
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Abnormal heart rhythm	1
Roxithromycin (Only on Non US Market)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	Bacterial infection	1
Sevoflurane	Ultane, Sojourn	Anesthesia	1
Sotalol	Betapace, Sotalex, Sotacor	Abnormal heart rhythm	1
Sparfloxacin (Removed from Market)	Zagam	Bacterial infection	1
Sulpiride (Only on Non US Market)	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Schizophrenia	1
Sultopride (Only on Non US Market)	Barnetil, Barnotil, Topral	Schizophrenia	1
Terfenadine (Removed from Market)	Seldane	Allergic rhinitis	1
Terlipressin (Only on Non US Market)	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss and others	Septic shock	1
Terodiline (Only on Non US Market)	Micturin, Mictrol (not bethanechol)	Bladder spasm	1
Thioridazine	Mellaril, Novoridazine, Thioril	Schizophrenia	1
Vandetanib	Caprelsa	Cancer (thyroid)	1

Drugs listed in Category 2 and 3 should be prescribed with caution (avoid if possible - if avoidance is not possible ensure QT is normal before commencing drug and that the patient has no other condition which is likely to prolong the QT).

Category 2:

Substantial evidence supports the conclusion that these drugs cause QT prolongation but there is insufficient evidence that they, when used as directed in labelling, have a risk of causing TdP

Generic Name	Brand Names (Partial List)	Therapeutic Use	Risk Category
Abarelix	Plenaxis	Cancer (prostate)	2
Alfuzosin	Uroxatral	Benign prostatic hyperplasia	2
Apalutamide	Erleada	Cancer (prostate)	2
Apomorphine	Apokyn, Ixense, Spontane, Uprima	Parkinson's disease	2
Aripiprazole	Abilify, Aripiprex	Schizophrenia, depression (adjunct)	2
Artemether + Lumefantrine	Coartem	Malaria	2
Artenimol+piperaquine (Only on Non US Market)	Eurartesim	Malaria	2
Asenapine	Saphris, Sycrest	Schizophrenia	2
Atomoxetine	Strattera	ADHD	2
Bedaquiline	Sirturo	Tuberculosis, Multi-drug resistant	2
Bendamustine	Treanda, Treakisym, Ribomustin, Levact	Leukemia, lymphoma	2
Benperidol (Only on Non US Market)	Anquil, Glianimon	Antipsychotic	2
Betrixaban	Bevyxxa	Anticoagulant	2
Bortezomib	Velcade, Bortecad	Cancer (multiple myeloma,lymphoma)	2
Bosutinib	Bosulif	Cancer (leukemia)	2
Buprenorphine	Butrans, Belbuca, Bunavail, Buprenex, Suboxone, Zubsolv	Narcotic addiction and pain	2
Cabozantinib	Cometriq	Renal cell carcinoma	2
Capecitabine	Xeloda	Cancer (GI, Breast)	2
Ceritinib	Zykadia	Cancer (Lung)	2
Clofazimine (Only on Non US Market)	Lamprene	Leprosy	2
Clomipramine	Anafranil	Depression	2
Clotiapine	Entumine	Psychosis	2
Clozapine	Clozaril, Fazaclo, Versacloz	Schizophrenia	2
Crizotinib	Xalkori	Cancer (Non-small cell lung cancer, metastatic)	2
Cyamemazine (cyamepromazine) (Only on Non US Market)	Tercian	Schizophrenia, sedation	2

Generic Name	Brand Names (Partial List)	Therapeutic Use	Risk Category
Dabrafenib	Tafinlar	Cancer (melanoma)	2
Dasatinib	Sprycel	Cancer (leukemia)	2
Degarelix	Firmagon, Ferring	Cancer (prostate)	2
Delamanid (Only on Non US Market)	Deltyba	Tuberculosis, drug resistant	2
Desipramine	Pertofrane, Norpramine	Depression	2
Deutetrabenazine	Austedo	Chorea (Huntington's disease	2
Dexmedetomidine	Precedex, Dexdor, Dexdomitor	Sedation	2
Dextromethorphan/Quinidine	Nuedexta	Pseudobulbar affect	2
Dolasetron	Anzemet	Nausea, vomiting	2
Efavirenz	Sustiva and others	HIV	2
Eliglustat	Cerdelga	Gaucher's disease	2
Encorafenib	Braftovi	Melanoma	2
Epirubicin	Ellence, Pharmorubicin, Epirubicin Ebewe	Cancer	2
Eribulin mesylate	Halaven	Cancer (breast, metastatic)	2
Ezogabine (Retigabine)	Potiga, Trobalt	Seizures, Partial	2
Felbamate	Felbatol	Epilepsy	2
Fingolimod	Gilenya	Multiple Sclerosis	2
Fluorouracil (5-FU)	Adrucil, Carac, Efudex, Efudix, others	Cancer	2
Flupentixol (Only on Non US Market)	Depixol, Fluanxol	Schizophrenia	2
Gemifloxacin	Factive	Bacterial infection	2
Glasdegib	Daurismo	Acute myeloid leukemia	2
Granisetron	Kytril, Sancuso, Granisol	Nausea, vomiting	2
Hydrocodone - ER	Hysingla™ ER, Zohydro ER	Pain, severe	2
Iloperidone	Fanapt, Fanapta, Zomaril	Schizophrenia	2
Imipramine (melipramine)	Tofranil	Depression	2
Inotuzumab ozogamicin	Besponsa	Acute Lymphocytic Leukemia	2
Isradipine	Dynacirc	Hypertension	2
Ketanserin (Only on Non US Market)	Sufrexal	Hypertension	2
Lacidipine	Lacipil, Motens	Hypertension	2
Lapatinib	Tykerb, Tyverb	Cancer (breast, metastatic)	2
Lenvatinib	Lenvima	Cancer (Thyroid)	2
Leuprolide	Lupron, Eligard, Viadur, Carcinil, Enanton, Leuplin, Lucrin,	Cancer (prostate)	2

Generic Name	Brand Names (Partial List)	Therapeutic Use	Risk Category
	Procren, Prostap and others		
Lithium	Eskalith, Lithobid	Bipolar disorder	2
Lopinavir and ritonavir	Kaletra, Aluvia	HIV/AIDS	2
Maprotiline	Ludiomil and others	Depression	2
Melperone (Only on Non US Market)	Bunil, Buronil, Eunerpan	Schizophrenia	2
Memantine	Namenda XR and many others	Alzheimer's disease	2
Midostaurin	Rydapt	Acute myeloid leukemia	2
Mifepristone	Korlym, Mifeprex	Pregnancy termination	2
Mirabegron	Myrbetriq	Bladder spasm	2
Mirtazapine	Remeron	Depression	2
Moexipril/HCTZ	Uniretic, Univasc	Hypertension	2
Necitumumab	Portrazza	Lung Cancer	2
Nicardipine	Cardene	Hypertension	2
Nilotinib	Tasigna	Cancer (leukemia)	2
Norfloxacin (Removed from US Market)	Noroxin, Ambigram	Bacterial infection	2
Nortriptyline	Pamelor, Sensoval, Aventyl, Norpress, Allegron, Noritren, Nortrilen	Depression	2
Nusinersen	Spinraza	Spinal Muscular Atrophy	2
Ofloxacin	Floxin	Bacterial infection	2
Osimertinib	Tagrisso	Cancer (EGFR pos. NSC Lung cancer)	2
Oxytocin	Pitocin, Syntocinon	Labor stimulation	2
Paliperidone	Invega, Xepilon	Schizophrenia	2
Palonosetron	Aloxi	Nausea	2
Panobinostat	Farydak	Multiple myeloma (Part of a 3 drug regimen)	2
Pasireotide	Signifor	Cushings Disease	2
Pazopanib	Votrient	Cancer (renal cell, sarcoma)	2
Perflutren lipid microspheres	Definity, Optison	Echocardiography	2
Perphenazine	Trilafon, Etrafon/Triavil, Decentan	Schizophrenia	2
Pilsicainide (Only on Non US Market)	Sunrythm	Arrhythmia	2
Pimavanserin	Nuplazid	Psychosis, Parkinson's Disease	2

Generic Name	Brand Names (Partial List)	Therapeutic Use	Risk Category
Pipamperone (Only on Non US Market)	Dipiperon (E.U), Propitan (Japan), Dipiperal, Piperonil, Piperonyl	Schizophrenia	2
Primaquine phosphate		Malaria	2
Promethazine	Phenergan	Nausea, vomiting	2
Prothipendyl (Only on Non US Market)	Dominal, Largophren, Timoval, Timovan, Tumovan	Schizophrenia	2
Ribociclib	Kisqali	Breast Cancer	2
Rilpivirine	Edurant, Complera, Eviplera	Viral infection (HIV/AIDS)	2
Risperidone	Risperdal	Schizophrenia	2
Romidepsin	Istodax	Lymphoma	2
Saquinavir	Invirase(combo)	Viral infection (HIV/AIDS)	2
Sertindole (Only on Non US Market)	Serdolect, Serlect	Schizophrenia, anxiety	2
Sorafenib	Nexavar	Cancer (liver, renal cell, metastatic thyroid)	2
Sunitinib	Sutent	Cancer (GIST, renal cell, pNET)	2
Tacrolimus	Prograf, Prograf, Advagraf, Protopic	Immune suppression	2
Tamoxifen	Nolvadex(discontinued 6/13), Istubal, Valodex	Cancer (breast)	2
Telavancin	Vibativ	Bacterial infection	2
Telithromycin	Ketek	Bacterial infection	2
Tetrabenazine	Nitoman, Xenazine	Chorea (Huntington's disease)	2
Tiapride (Only on Non US Market)	Tiapridal, Italprid, Sereprile, Tialaread, Tiaryl, Tiaprim, Tiaprizal, Sereprid, Tiapridex	Alcoholism, withdrawal	2
Tipiracil and Trifluridine	Lonsurf	Metastatic colorectal cancer	2
Tizanidine	Zanaflex, Sirdalud	Muscle spasticity	2
Tolterodine	Detrol, Detrusitol	Bladder spasm	2
Toremifene	Fareston	Cancer (breast, metastatic)	2
Tramadol	Crispin, Ralivia ER, Ralivia Flashtab, Tramadolum, Tramal, Tramodol, Tridural, Ultram, Ultram ER, Zydol	Pain	2
Trimipramine	Surmontil, Rhotrimine, Stangyl	Depression	2
Tropisetron (Only on Non US Market)	Navoban, Setrovel	Nausea, vomiting	2

Generic Name	Brand Names (Partial List)	Therapeutic Use	Risk Category
Valbenazine	Ingrezza	Tardive Dyskinesia	2
Vardenafil	Levitra	Erectile dysfunction	2
Vemurafenib	Zelboraf	Cancer (melanoma)	2
Venlafaxine	Effexor, Efexor	Depression	2
Vorinostat	Zolinza	Cancer (lymphoma)	2
Zotepine	Losizopilon, Lodopin, Setous and Zoleptil	Schizophrenia	2
Zuclopenthixol, Zuclopentixol	Cisordinol, Clopixol, Acuphase	Psychosis	2

Category 3: Substantial evidence supports the conclusion that these drugs prolong QT and have a risk of TdP but only under certain known conditions (e.g. excessive dose, drug interaction, etc.)

Generic Name	Brand Names (Partial List)	Therapeutic Use	Risk Category
Amantadine	Symmetrel, Symadine	Viral infection (Influenza), Parkinson's disease	3
Amisulpride (Only on Non US Market)	Solian, Supitac, Soltus, Amitrex, Amazeo	Schizophrenia	3
Amitriptyline	Elavil (Discontinued 6/13), Tryptomer, Tryptizol, Laroxyl, Saroten, Sarotex Lentizol, Endep	Depression	3
Amphotericin B	Fungilin, Fungizone, Abelcet, AmBisome, Fungisome, Amphocil, Amphotec	Fungal infection	3
Amsacrine (acridinyl anisidide)	Amsidine	Acute Lymphoblastic Leukemia	3
Atazanavir	Reyataz, Evotaz	Viral infection (HIV/AIDS)	3
Bendroflumethiazide or bendrofluazide (Only on Non US Market)	Aprinox	Hypertension, diuresis	3
Chloral hydrate	Aquachloral, Novo-Chlorhydrate, Somnos, Noctec, Somnote	Sedation, insomnia	3
Cimetidine	Tagamet and others	Gastric hyperacidity, Gastroesophageal reflux disease (GERD)	3
Diphenhydramine	Benadryl, Nytol, Unisom, Sominex, Dimedrol, Daedalon	Allergic rhinitis, insomnia	3

Generic Name	Brand Names (Partial List)	Therapeutic Use	Risk Category
Doxepin	Sinequan, Silenor, Aponal, Adapine, Doxal, Deptran, Sinquan	Depression	3
Eperisone	Myonal, Epry	Spasticity	3
Esomeprazole	Nexium, Nexum and others	Gastric hyperacidity, GERD	3
Famotidine	Pepcid, Fluxid, Quamatel	Gastric hyperacidity, GERD	3
Fluoxetine	Prozac, Sarafem, Fontex	Depression	3
Fluvoxamine	Faverin, Fevarin, Floxyfral, Dumyrox and Luvox	Depression, Obsessive Compulsive Disorder	3
Furosemide (frusemide)	Lasix, Fusid, Frumex	Hypertension, diuresis	3
Galantamine	Reminyl, Nivalin, Razadyne-ER, Lycoremine	Dementia (Alzheimer's Disease)	3
Garenoxacin (Only on Non US Market)	Geninax	Bacterial infection	3
Hydrochlorothiazide	Apo-Hydro, Aquazide H, BP Zide, Dichlotride, Hydrodiuril, HydroSaluric, Hydrochlorot, Microzide, Esidrex, Oretic	Hypertension, diuresis	3
Hydroxychloroquine	Plaquenil, Quineprox	Malaria, SLE, rheumatoid arthritis	3
Hydroxyzine	Atarax, Vistaril, Aterax, Alamon, Durrax, Equipose, Masmoran, Orgatrax, Paxistil Quiess, Tran-Q, Tranquizine	Allergic reaction, anxiety disorders	3
Indapamide	Lozol, Natrilix, Insig	Hypertension, diuresis	3
Itraconazole	Sporanox, Onmel	Fungal infection	3
Ivabradine	Procoralan, Coralan, Corlentor, Coraxan, Ivabid, Bradia	Angina Pectoris (heart pain)	3
Ketoconazole	Nizoral, Sebizole, Ketomed, Keton	Fungal infection	3
Lansoprazole	Prevacid	Proton-pump inhibitor	3
Loperamide	Imodium and many other OTC and Rx brands	Diarrhea	3
Metoclopramide	Reglan, Afipran, Maxolon, Cerucal, Clopamon, Clopra, Maxeran, Maxolon, Metozolv, Plasil, Pramin, Primperan, Perinorm	Nausea, vomiting	3

Generic Name	Brand Names (Partial List)	Therapeutic Use	Risk Category
Metolazone	Zytanix, Zaroxolyn, and Mykrox	Hypertension	3
Metronidazole	Flagyl and many others	Trichomoniasis, amebiasis, bacterial infection	3
Nelfinavir	Viracept	Viral infection (HIV/AIDS)	3
Olanzapine	Zyprexa, Zydis, Relprevv	Schizophrenia, bipolar disorder	3
Omeprazole	Losec, Prilosec, Zegerid	Gastric hyperacidity, GERD	3
Pantoprazole	Protonix and others	Gastric hyperacidity, GERD	3
Paroxetine	Paxil, Aropax, Pexeva, Seroxat, Sereupin, Seroxat	Depression	3
Piperacillin/Tazobactam	Tazosyn and Zosyn	Bacterial infection	3
Posaconazole	Noxafil, Posamol	Fungal infection	3
Propafenone	Rythmol SR, Rytmonorm	Abnormal heart rhythm	3
Quetiapine	Seroquel	Schizophrenia	3
Quinine sulfate	Qualaquin	Malaria, leg cramps	3
Ranolazine	Ranexa, Ranozex	Angina Pectoris (heart pain)	3
Sertraline	Zoloft, Lustral, Daxid, Altruline, Besitran, Deprax, Elrval, Emergen, Gladem, Implicane, Sedoran, Sealdin, SerivoLowfin, Stimuloton, Tresleen, Sertralin Bluefish	Depression	3
Solifenacin	Vesicare	Bladder spasm	3
Telaprevir	Incivo, Incivek	Viral infection (hepatitis C)	3
torsemide (torasemide)	Demadex, Diuver, Examide	Hypertension, diuresis	3
Trazodone	Desyrel (discontinued 6/13), Oleptro, Beneficat, Deprax, Desirel, Molipaxin, Thombran, Trazorel, Trialodine, Trittico, Mesyrel	Depression, insomnia	3
Voriconazole	VFend	Fungal infection	3
Ziprasidone	Geodon, Zeldox	Schizophrenia	3

17.5 APPENDIX 4: MANAGEMENT OF EYE TOXICITY

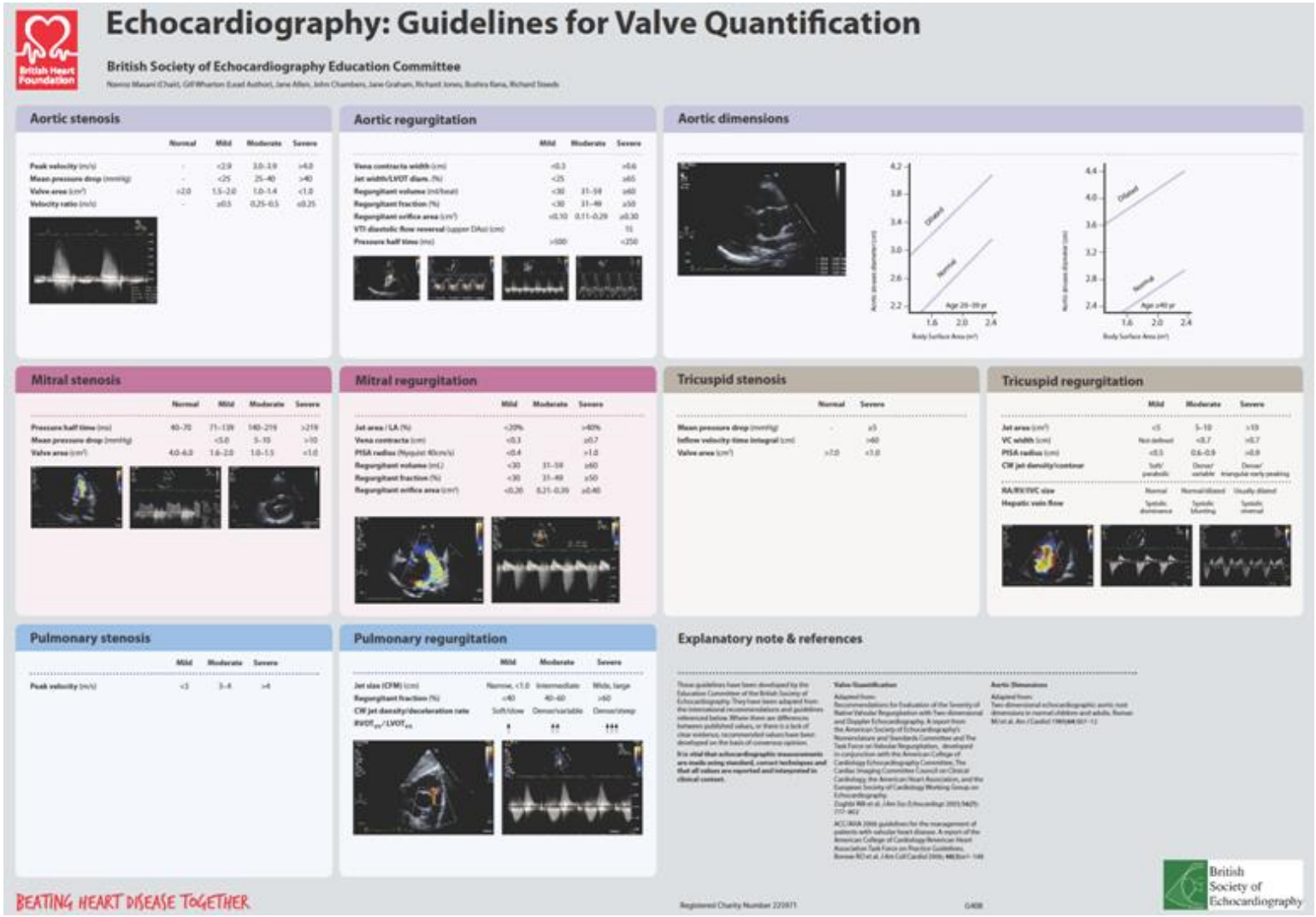
If the patient reports any changes in vision during the course of the trial and between the scheduled assessments or any changes are noted during best correct visual acuity tests, a full assessment by ERG will be instigated.

If a 25% (or more) a-wave reduction and/or a 50% (or more) b-wave reduction on ERG is recorded, dosing with AZD3965 will be interrupted. ERG assessments will be repeated within 14 days and if the changes have not resolved to baseline or less than 25% and 50% respectively within 2 weeks following dose delay the patient will be withdrawn from the study.

If a 50% (or more) a-wave reduction on ERG is recorded, dosing with AZD3965 will be stopped immediately and the patient withdrawn from the study.

If a patient is withdrawn from the study due to eye toxicity, repeat ERG examinations will be repeated within 14 days and performed at least monthly thereafter or until resolution or return to baseline.

17.6 APPENDIX 5: Severe valvular heart disease (as defined by British Society of Echocardiography)



http://www.bsecho.org/media/40509/valve-final-2011_2_.pdf