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Sponsor Protocol Number	CRUKD/16/001
Official Title	A Cancer Research UK Phase I/IIa clinical trial of BI-1206; an antibody to FcγRIIB (CD32b), as a single agent and in combination with an anti-CD20 antibody in patients with CD32b positive B-cell malignancy
Document, Version & Date	Protocol Version 10, dated 03 September 2019

CANCER RESEARCH UK

Centre for Drug Development

A CANCER RESEARCH UK PHASE I/IIA CLINICAL TRIAL OF BI-1206; AN ANTIBODY TO FCγRIIB (CD32B), AS A SINGLE AGENT AND IN COMBINATION WITH AN ANTI-CD20 ANTIBODY IN PATIENTS WITH CD32B POSITIVE B-CELL MALIGNANCY.

Sponsor protocol number: CRUKD/16/001

EudraCT number: 2015-004999-29

Chief Investigator: Prof Andrew Davies
Southampton General Hospital
[redacted]

Sponsor: Cancer Research UK
Centre for Drug Development
[redacted]

PARTICIPATING INVESTIGATORS AND CENTRES:

Details of Principal Investigators and Investigational Sites are recorded on the Participating Investigators and Centres list in the Sponsor's Trial Master File.

VERSION HISTORY:

Version No.	Version Date	Reason for update
1	07-Apr-2016	Initial version submitted for Regulatory and Ethics approval
2	26-May-2016	Sections 4.12, 5, 7.6.1, 9.6.3 and 11 updated in response to MHRA request including addition of Section 5.3 Communication Plan where dose escalation is to occur and extension of safety follow-up to 125 days.
3	04-Jul-2016	Section 6.2.5 updated to amend shelf life of diluted drug to 24 hours for first dose level. Other non-substantial changes made.
4	02-Feb-2017	Sections 7.1.3 and 7.7 updated to include to oxygen saturation levels (SaO2) at baseline, prior to infusion during week 1-4 (induction period) and otherwise as clinically indicated. Eye examination to be performed within 4 weeks of first dose at screening. Patients in cohort will be seen on Day 25 (Week 4 day 4). Sections 7.7, 8.1.1, 8.4.1, 8.4.3 and 8.4.4 updated to include 2 additional PD samples on days 2 and 4 of weeks 1-4. Emerging data will be reviewed at dose review meetings and a decision made for the following cohort as to whether or not these samples are required. PD sample [redacted] has been also reduced to 6mL. Other non-substantial changes made.
5	09-Jun-2017	Non- substantial amendment - Clarification that Cohort 1 consists of a minimum of one patient and is consistent with other sections of the protocol. - Clarification that tumour assessment in the maintenance phase is every 16 weeks and is consistent with other sections of the protocol. Other non-substantial changes made.
6	25-Jan-2018	Section 4.1.2 updated to reflect clarifications and changes to the eligibility criteria. Section 5.7.2 updated to clarify alternative pre-medication steroids for infusion related reactions may be used if deemed clinically appropriate by Investigator, CI, and Sponsor. Other non-substantial changes made.
7 (Not implemented)	10-Jul-2018	Change to the trial design to bring forward combination dose escalation (Arm 2) in Part A.

		Change to the starting dose and dose increments of BI-1206 to be administered in combination with rituximab (Arm 2) in Part A. Once the combination dose escalation arm (Part A, Arm 2) is opened, it will run in parallel to the single agent dose escalation arm (Part A, Arm1), dose decisions and cohort size decisions will be made independently from data within the arm, however available data from the other arm and any available data from other trials investigating BI-1206 will be taken into consideration. Clarification that the RP2D of single agent BI-1206 determined in Part A, Arm 1 and RP2D of combination dose of BI-1206 and rituximab determined in Part A, Arm 2 may differ, but will not exceed 800 mg. Dose escalation cohorts in both Arm 1 and Arm 2 of Part A may include a minimum of one patient, if supported by emerging safety data and agreed in the dose decision meeting prior to next cohort opening. Any ≥ Grade 2 related toxicity in one patient will expand the cohorts to a 3+3 patient cohort. All patients recruited to the combination arms of the trial will be given rituximab at a dose of 375 mg/m^2 and follow the same dosing schedule. Rituximab biosimilars are permitted in the trial. PK/PD sampling schedule updated to reflect combination dose escalation (Arm 2) in Part A. Other non-substantial changes and corrections made.
8	20-Sep-2018	CTA amendment 12 (incorporating Protocol version 7.0) was not approved by the MHRA. CTA amendment 13 (incorporating Protocol version 8.0) includes the changes from Protocol version 7.0 plus additional updates to Sections 5.3.2, 5.3.4, Table 1, 5.4.1, 5.4.2, Figure 4, 5.4.3 and 4.2 to address the GNA (grounds for non-acceptance) raised: - Clinically relevant Grade 2 or higher related toxicity will trigger cohort expansion from a minimum of one patient to 3+3 cohorts; no option to revert back to single patient cohorts once expanded. - Statement added to clarify treatment arm allocation (in addition to dose level) will be confirmed and assigned by the Sponsor in the registration email. Section 4.1.2 , Exclusion criteria 7 corrected to clarify that certain ≤Grade 2 toxicities, which in the opinion of the Investigator and the Sponsor, should not exclude the patient from participation in the study. Other non-substantial changes and corrections made.

9	20-Mar-2019	Non-substantial amendment: [redacted] The number and total volume of blood samples for pharmacodynamic analysis [redacted] required during Week 1 – Week 4 has been reduced. A ± 5 minute time window has been added for the measurement of vital signs at the end of infusion. Clarification that drug-related SAEs after the 125-day period reporting is are required even if the patient has started another anti-cancer therapy. Other non-substantial changes made.
10	03-Sep-2019	Substantial amendments: - Part A of the study: Remove eligibility requirement for CD32b positivity but continue to assess CD32b expression for information only. - Allow split dosing of BI-1206 +/- rituximab from Week 1 if clinically indicated. - Additional assessments in Week 1 to monitor platelet counts and liver transaminases. - Clarification of dosing intervals, modifications and acceptable dose delays for logistical/ operational reasons. - Clarification of patient evaluability for dose escalation decisions. - Clarifications/revisions to inclusion/exclusion criteria. - Revision/addition of tertiary endpoints to align with the amendment and include additional biomarker work. - Other administrative/minor non-substantial changes.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
A	ABPI	Association of the British Pharmaceutical Industry
	ADA	anti-drug antibody
	ADCC	antibody dependent cell-mediated cytotoxicity
	ADCP	antibody dependent cellular phagocytosis
	AE	adverse event
	AL	Amyloidosis
	ALT	alanine aminotransferase
	ANA	antinuclear antibody
	ANC	absolute neutrophil count
	AST	aspartate aminotransferase
	AUC	area under the curve
B	BP	blood pressure
	BSA	body surface area
C	CDD	Centre for Drug Development
	CD32b+	CD32b (FcγRIIB) positive
	CHOP	cyclophosphamide, vincristine and doxorubicin chemotherapy
	CI	Chief Investigator
	CLL	chronic lymphocytic leukaemia
	CLT	total body clearance
	C_{max}	maximum observed serum concentration
	CR	complete response
	CRA	Clinical Research Associate
	CRS	cytokine release syndrome
	CRR	complete response rate
	CRUK	Cancer Research UK
	CSM	Clinical Study Manager
	CT	computerised tomography
	CTA	clinical trial authorisation
	CTCAE	Common Terminology Criteria for Adverse Events
D	Day	calendar day
	DCF	data clarification form
	DLBCL	diffuse large B cell lymphoma
	DLT	dose limiting toxicity
E	ECG	electrocardiogram
	eCRF	electronic case report form
	ED_{10}	effective dose
	EDC	electronic data capture
	EDTA	ethylene diamine tetra-acetic acid
	ELISA	enzyme-linked immunosorbent assay
	EORTC	European Organisation for Research and Treatment of Cancer
	EPD	early progression
F	FCɣRIIB	Fc gamma receptor 2b
	FBC	Full blood count
	FDG	fluorodeoxyglucose
	FIH	first in human
	FL	follicular lymphoma
	FU	Formulation Unit
G	GCP	Good Clinical Practice
	GLP	Good Laboratory Practice

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
	GMP	Good Manufacturing Practice
H	h	hour
	Hb	haemoglobin
	HCG	human chorionic gonadotropin
	HIV	human immunodeficiency virus
I	IB	Investigator's Brochure
	ICD	informed consent document
	ICH GCP	International Conference on Harmonisation of Good Clinical Practice
	IHC	immunohistochemistry
	IMP	investigational medicinal product
	INR	international normalised ratio
	IRR	infusion related reaction
	ITF	Investigator Trial File
	IV	intravenous
K	Kd	disassociation constant
L	LDH	lactate dehydrogenase
M	MABEL	minimum anticipated biological effect level
	mAb	monoclonal antibody
	MAD	maximum administered dose
	MCL	mantle cell lymphoma
	MIA	manufacturing authorisation holder
	min	minute(s)
	MHRA	Medicines and Healthcare products Regulatory Agency
	MRT	mean residence time
	MTD	maximum tolerated dose
N	NCI	National Cancer Institute
	NaCl	sodium chloride
	NHL	Non-Hodgkin lymphoma
	NOAEL	no observed effect level
	NYHA	New York Heart Association
O	ORR	overall response rate
	OS	overall survival
P	PAD	pharmacologically active dose
	PCD	programmed cell death
	PCR	Polymerase chain reaction
	PD	progressive disease
	PET	positron emission tomography
	PES	polyether sulfone
	PI	Principal Investigator
	PK	pharmacokinetic
	PK/PD	pharmacokinetic/pharmacodynamic
	PFS	progression free survival
	PML	progressive multifocal leukoencephalopathy
	PR	partial response
	PSRB	Protocol and Safety Review Board
	PT	prothrombin time
	PTT	partial thromboplastin time
	PVC	polyvinyl chloride
Q	QA	quality assurance
	QC	quality control
	QP	Qualified Person

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
R	RA	rheumatoid arthritis
	REC	Research Ethics Committee
	RNA	Ribonucleic acid
	RO	receptor occupancy
	RP2D	recommended Phase II dose
	RSI	reference safety information
S	SAE	serious adverse event
	SD	stable disease
	SDV	source data verification
	SLL	small lymphocytic leukaemia
	SOP	standard operating procedure
	SmPC	Summary of Product Characteristics
	SaO2	Oxygen saturation - amount of oxygenated haemoglobin in the blood
	SUSAR	suspected unexpected serious adverse reaction
T	$T_{1/2}$	terminal elimination half-life
	T_{max}	time to reach C_{max}
	TLS	tumour-lysis syndrome
	TSH	thyroid stimulating hormone
U	ULN	upper limit of normal
	USM	urgent safety measure
V	V_{SS}	steady state volume of distribution
W	WBC	white blood cell
	WHO	World Health Organisation
	WMA	World Medical 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 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 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

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1 PROTOCOL SYNOPSIS

Full title: A Cancer Research UK Phase I/IIa clinical trial of BI-1206; an antibody to FcγRIIB (CD32b), as a single agent and in combination with an anti-CD20 antibody in patients with CD32b positive B-cell malignancy

Short title: BI-1206 and an anti-CD20 antibody in patients with CD32b positive B-cell lymphoma or leukaemia.

Clinical trial objectives and endpoints:

Primary objectives	Endpoints
Part A Escalation phase	
Arm 1: To propose a recommended dose for Phase II evaluation of BI-1206 as a single agent by:	
(a) Establishing the maximum tolerated dose (MTD) or maximum administered dose (MAD) of BI-1206 given once weekly for four weeks, via intravenous infusion in patients with relapsed or refractory B-cell malignancies.	(a) Determining the maximal dose (up to 800 mg) of BI-1206 at which no more than one patient out of up to six patients at the same dose level experience a highly probably or probably BI-1206 related dose-limiting toxicity during induction therapy and up to one week post the fourth infusion.
(b) Assessing the safety and toxicity profile of BI-1206 as a single agent.	(b) Documenting adverse events (AEs), serious adverse events (SAEs) (graded according to NCI- CTCAE Version 4.02) and laboratory parameters and determining their causality in relation to BI-1206. Causality of AEs/SAEs will be assessed by the Investigator.
Arm 2: To propose a recommended dose for Phase II evaluation of BI-1206 in combination with an anti-CD20 antibody by:	
(c) Establishing the MTD or MAD of BI-1206 and an anti-CD20 antibody given once weekly for four weeks, via intravenous infusion in patients with relapsed or refractory B-cell malignancies.	(c) Determining the maximal dose (up to 800 mg) of BI-1206 at which no more than one patient out of up to six patients at the same dose level experience a highly probably or probably BI-1206 or anti-CD20 antibody-related dose-limiting toxicity during induction therapy and up to one week post the fourth infusion.
(d) Assessing the safety and toxicity profile of BI-1206 in combination with an anti-CD20 antibody.	(d) Documenting AEs, SAEs (graded according to NCI-CTCAE Version 4.02) and laboratory parameters and determining their causality in relation to BI-1206 and, where appropriate, anti-CD20 antibody. Causality of AEs/SAEs will be assessed by the Investigator.
Part B Expansion phase	
Assessing the safety and toxicity profile of: • BI-1206 as a single agent in Arm 1 at the RP2D as determined in Part A (Part B, Arm1). • BI-1206 when given in combination with an anti-CD20 monoclonal at the RP2D combination dose as determined in Part A (Part B, Arm 2).	Documenting AEs, SAEs (graded according to NCI-CTCAE Version 4.02) and laboratory parameters and determining their causality in relation to BI-1206 and, where appropriate, anti-CD20 antibody. Causality of AEs/SAEs will be assessed by the Investigator.

The secondary and tertiary objectives and endpoints of the trial can be found in Sections 3.1.2 and 3.1.3.

Study Design:

This is a multi-centre, dose escalation, first in human (FIH) Phase I/IIa trial in patients withB-cell malignancy. The clinical trial is in two parts (see Figure 2):

Part A: The first part of the study will be a dose escalation stage conducted in two arms:

- **Arm 1 (single agent):** Dose escalation phase to determine the MTD or MAD and recommended Phase II dose (RP2D) of BI-1206 administered as a single agent.
- **Arm 2 (combination):** Dose escalation phase to determine the MTD or MAD and RP2D of BI-1206 administered in combination with an anti-CD20 antibody. Rituximab has been chosen as the most appropriate anti-CD20 antibody (see Sections 2.2.6 and 2.2.7).

Part B: The second part of the study will be a dose expansion stage conducted in two arms, in patients with CD32b positive (CD32b+) B-cell malignancy:

- **Arm 1 (single agent):** Expansion cohort of up to 25 patients administered single agent BI-1206 at the RP2D as determined in Part A, Arm 1. This expansion will include a minimum of 12 chronic lymphocytic leukaemia (CLL) and six mantle cell lymphoma (MCL) patients. Part B, Arm 1 will be able to open once a RP2D in Part A Arm 1 is established.
- **Arm 2 (combination):** Expansion cohort of up to 25 patients at the identified RP2D as determined in Part A, Arm 2 that can be given with an anti-CD20 antibody. Rituximab has been chosen as the most appropriate anti-CD20 antibody (see Sections 2.2.6 and 2.2.7). This expansion will include a minimum of 12 CLL and six MCL patients. Part B, Arm 2 will be able to open once a RP2D in Part A Arm 2 is established.

Study treatment:

BI-1206 will be administered by (intravenous) IV infusion to all patients once weekly for a period of four weeks, which will be classified as induction therapy. The starting dose of BI-1206 will be 0.4 mg (Week 1).

When BI-1206 and rituximab are given in combination (Arm 2 in Parts A and B), the rituximab infusion will be given after the BI-1206 infusion at a dose consistent with the Summary of Product Characteristics (SmPC) of rituximab (375 mg/m^2).

For patients who show clinical benefit at Week 8 (as defined in Section 10.2), a period of maintenance therapy may be given. A patient's maintenance therapy will be given at the same dose (single agent BI-1206 or combination) as their induction therapy and will be given once every eight weeks for a period of up to one year, following their first dose of BI-1206 or combination treatment on the trial.

Patient Population:

Up to 81 evaluable patients with B-cell malignancies will be entered into this trial.

In Part A, Arm 1 (single agent dose escalation), it is estimated that up to 19 patients will be required to establish the BI-1206 single agent RP2D. In Part A, Arm 2 (combination dose escalation), it is estimated that up to 15 patients will be required to establish the BI-1206 combination RP2D.

In Part B, approximately 40-50 patients will be recruited in the expansion arms (to include a minimum of 24 CLL and 12 MCL patients). The final number of patients in the trial overall will depend upon the number of dose escalations required to identify the single agent RP2D (Part A, Arm 1) and the RP2D combination dose (Part A, Arm 2) [1].

2 INTRODUCTION

2.1 Background

2.1.1 B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia.

The B-cell malignancies B-cell non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukaemia (CLL) are the most common types of haematological malignancy. NHL is the sixth most common cancer in the UK, with B-cell lymphomas (including follicular lymphoma [FL], diffuse large B-cell lymphoma [DLBCL] and mantle cell lymphoma [MCL] among others) accounting for 85% of all NHLs [2]. In the United Kingdom this equates to over 10,000 cases in 2012 [3].

The most substantial advancement in the treatment of B-cell malignancies, since the advent of combination chemotherapy, has been the addition of the monoclonal anti-CD20 antibody rituximab (Rituxan™). Since its initially reported single-agent activity in indolent lymphomas in 1997, the role of rituximab has expanded to cover both indolent and aggressive lymphomas. Rituximab has become firmly incorporated in the therapy of patients with follicular and other indolent lymphomas in combination with chemotherapy. Furthermore, maintenance therapy with rituximab is being employed to delay time to disease progression [4]. Undoubtedly, the advent of rituximab has contributed to the observed improved survival in FL [5-7]. Many patients will however demonstrate resistance to therapies that include rituximab or will relapse following rituximab exposure. For these patients, effective options are limited. The median survival period for patients with relapsed and refractory B-cell lymphoma treated with rituximab is approximately 13 months [8, 9].

Chronic lymphocytic leukaemia is a B-cell malignancy characterised by a progressive accumulation of functionally incompetent lymphocytes in the peripheral blood. It is the most common form of leukaemia found in adults in the Western World, with an annual incidence of approximately six cases per 100,000, mainly affecting the elderly population [10]. The onset of the disease may be insidious and the clinical course variable. Fludarabine based combination regimens are increasingly used as initial treatment in a limited population of fit patients [11] and the addition of rituximab to combination chemotherapy has resulted in improved outcomes [12]. Despite recent developments in the treatment of CLL, challenges remain for those patients refractory to fludarabine regimens or to those who are not suitable for this treatment, where the median survival is approximately 12 months [13].

Despite recent therapeutic advances, CLL remains incurable and there is a clinical need for new treatment options, in the management of advanced disease.

2.1.2 CD32b and BI-1206

CD32b (also known as FcγRIIB) is a cell surface receptor whose expression in adults is restricted to myeloid (e.g. macrophages, dendritic, Langerhan and mast cells) and lymphoid cells (B cells); but not natural killer (NK) cells [14-17]. CD32b is a physiological regulator of humoral immunity and plays a role in maintaining B-cell tolerance in the periphery [18, 19]. As the sole inhibitory hFcγR, CD32b negatively regulates immune cell responses to endogenous and therapeutic antibodies by counteracting signals from the activating FcγRs (CD64, CD32a, CD32c, and CD16) [20, 21].

Preclinical studies have shown that loss of CD32b increases the efficacy of therapeutic antibodies [16, 17, 22]. This observation has been corroborated in the clinic where multiple studies have demonstrated that high CD32b expression levels correlate positively with poor prognosis and inversely with success of rituximab therapy in FL and MCL [23, 24]. [redacted]

BI-1206 is a fully human IgG1 antibody, developed by BioInvent International AB. The target antigen, FcγRIIB (also known as CD32b), is a single transmembrane receptor expressed on immune cells [25, 26]. CD32b is expressed at high levels by lymphomas and leukaemias of B cell origin including MCL,

CLL/ small lymphocytic (SLL) and to a lesser extent FL as well as diffuse large B-cell lymphoma (DLBCL) [27]. CD32b is also expressed on immune effector cells [28].

2.2 Investigational medicinal product

2.2.1 Structure of BI-1206

BI-1206 is a human IgG1 antibody that targets human CD32b.

2.2.2 Mechanism of action of BI-1206

[redacted]

2.2.3 Non-clinical anti-tumour activity

[redacted]

- [redacted]

[redacted]

[redacted]

2.2.4 Safety considerations for the proposed trial

2.2.4.1 BI-1206 Toxicology

BI-1206 demonstrates extremely specific binding to human FcγRIIB (hFcγRIIB, also known as CD32b) and does not cross react with even closely related human proteins such as FcγRIIA or FcγRIIB from other animal species; consequently there are no relevant animal toxicology test species available to evaluate the safety of this antibody.

Studies have been performed to assess the potential for cytokine release syndrome (CRS) with BI-1206 and despite CD32b expression being restricted to myeloid and lymphoid cells there is no evidence that BI-1206 is capable of inducing cytokine release from whole blood *in vitro*.

[redacted]

[redacted]

[redacted]

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

A summary of the safety considerations and mitigation strategies for this trial is provided in Section 2.2.8.

For additional information concerning BI-1206, please refer to the Investigator Brochure. The non-clinical package and proposed approach for setting the starting dose for this study was discussed with the MHRA at a scientific advice meeting [redacted]

2.2.5 Clinical experience (other compounds targeting CD32b)

This proposed clinical trial is a first in human (FIH) study of BI-1206 a human IgG1 anti CD32b monoclonal antibody and as such there is no existing clinical experience with this product.

In 2015 Xencor commenced evaluation of XmAb5871 a monoclonal antibody that targets CD19 with its variable domain and an immune inhibitory Fc domain to target FcγRIIb in patients with rheumatoid arthritis (RA). Initial results of a Phase Ib/II, randomised, double-blinded, placebo-controlled study in patients with RA have been reported [33]. Patients received six IV infusions of XmAb5871 or placebo

on an every 14 day schedule. In Part A, 30 RA patients were randomised to placebo or XmAb5871 in four consecutive dose cohorts of 0.3, 1, 3, or 10 mg/kg. After completion of Part A, 27 patients with active RA were enrolled in an extension cohort, Part B, to receive either 10 mg/kg XmAb5871 or placebo in a 2:1 ratio. A total of 57 patients were randomised; 40 patients received at least 1 dose of XmAb5871. The peripheral B cell count decreased ~40% from baseline after the first dose in all XmAb5871 cohorts and did not decrease further with subsequent doses. XmAb5871 was generally well tolerated, with two serious adverse events (SAEs) reported in the XmAb5871 group (infusion-related reaction, venous thrombosis). The most common treatment-related adverse events in the XmAb5871 group were nausea, vomiting or diarrhoea which occurred only during the first infusion in 25% of patients. Two subjects experienced infusion reactions with hypotension (both at 10 mg/kg) and were discontinued. The nature and severity of these infusion reactions were consistent with those reported for other monoclonal antibody therapies. The researchers concluded XmAb5871 administered over 12 weeks was generally well tolerated. Although the trial was not powered to show a significant difference in efficacy results between XmAb5871 and placebo, sufficient efficacy trends were seen to warrant continued clinical development of XmAb5871 in autoimmune diseases.

The only other CD32b targeted antibody currently being evaluated in clinical trials at the time of writing this protocol appears to be the CD32b x CD79b Dual Affinity Re-Targeting (DART®) Bi-specific Antibody-Based Molecule: MGD010 being developed by MacroGenics. In February 2015, MacroGenics initiated a Phase I study in healthy volunteers with this agent (Clinical trials.gov identifier NCT023760360).

No other trials have been conducted using a CD32b targeted monoclonal antibody, however the use of monoclonal antibodies (such as rituximab) in the treatment of B-cell malignancies is routine practice and a number of trials have been performed or are ongoing using fully human or humanised IgG1 antibodies similar to BI-1206.

For further details on other compounds targeting CD32b or any other trials that have been developed to investigate BI-1206, refer to BI-1206 Investigators Brochure (IB). At the start of the clinical trial, the information referenced from the IB was current. Updates to the IB will not be reflected in this section so refer to the current version of the IB for up to date information.

2.2.6 Background on rituximab

The choice of rituximab (and approved biosimilars, see Section 2.2.7) as the combination agent for this study has been made in the context of a clinical landscape for treatment of B-cell malignancies that is rapidly evolving. Notably the third generation anti-CD20 antibody, obinutuzumab, has shown promising results in clinical trials [34, 35]. Obinutuzumab has received EMA approval for use as a first line treatment for CLL in combination with chlorambucil [36, 37] but it is not currently available in the UK for treatment of relapsed/refractory CLL or for the treatment of other B-cell malignancies. Additionally, the mechanisms by which the efficacy of rituximab is reduced have been much better elucidated than for obinutuzumab[38]. Rituximab has therefore been chosen as the most appropriate anti-CD20 antibody for use in combination at the start of this study.

The human anti-CD20 monoclonal antibody (mAb) rituximab was the first mAb approved for cancer immunotherapy, and has been widely administered to patients with B-cell cancers including FL, DLBCL, CLL, and MCL. Currently, rituximab is approved in Europe as induction therapy in combination with chemotherapy for patients with Stage III-IV FL who are previously untreated, as well as maintenance therapy in those responding to induction therapy; it is also approved as monotherapy for patients who are chemoresistant or are in their second or subsequent relapse after chemotherapy. Rituximab is also approved for the treatment of patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, vincristine and doxorubicin) chemotherapy. In lymphoma the standard rituximab dose is 375 mg/m^2. In CLL, rituximab is approved for the treatment of patients with previously untreated and relapsed/refractory CLL at a standard dose of 500 mg/m^2.

For the purposes of this clinical trial, rituximab will be classed as an investigational medicinal product (IMP) and all patients recruited in Arm 2, including CLL patients, will be treated with a standard rituximab dose of 375 mg/m^2.

The toxicities associated with rituximab are described in the SmPC for this agent (included in the IB Package). Based on data for patients with NHL and CLL from clinical trials and from post-marketing surveillance, the most frequently observed adverse events in patients receiving rituximab are infusion-related reactions (such as infusion reaction, cytokine release syndrome [CRS] and tumour-lysis syndrome [TLS]) which occur in >50% of patients, and are predominantly seen during the first infusion, usually in the first one to two hours following the start of administration. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1% after eight doses of the drug. Infectious events (predominantly bacterial and viral) occurred in 30 to 55 % of patients during clinical trials in patients with NHL and in 30 to 50 % of patients with CLL. The most frequently reported or observed serious adverse drug reactions were, infusion-related reactions (including CRS and TLS), infections and cardiovascular events. Other common undesirable effects associated with rituximab include: neutropenia, leucopenia, plus febrile neutropenia and thrombocytopenia, angioedema, pruritus, rash and alopecia, nausea, fever, chills, asthenia, headache and decreased IgG levels. Of note, results of the PRIMA trial examining long term maintenance therapy with rituximab did not demonstrate a significant decrease in IgG levels with long-term maintenance therapy of rituximab.

2.2.7 Rituximab Biosimilars

Rituximab was first marketed in Europe under the brand name MabThera®. More recently, rituximab biosimilars have been launched (e.g. Rixathon® and Truxima®). It should be noted rituximab biosimilars may be used in this clinical trial (**Sponsor must be notified prior to use)** since they are licensed for use in the same indications and have the same expected safety profile as the originator product MabThera®. Therefore, any reference to rituximab throughout this protocol refers to both the originator product, MabThera® or an approved rituximab biosimilar.

For additional information concerning rituximab (or rituximab biosimilar), please refer to the SmPC specific to the brand used.

The rituximab SmPC included in the IB Package supplied for use in this trial is defined as the reference safety information (RSI) for all brands of rituximab used in this trial.

2.2.8 Expected safety profile for BI-1206 ± rituximab

Based on preclinical experience with BI-1206 alone and in combination with anti-CD20 antibodies (such as rituximab), emerging clinical data from the ongoing CRUKD/16/001 trial, reported clinical data regarding XmAb5871 and clinical experience of rituximab therapy, the potential toxicities associated with BI-1206 ± rituximab therapy could include the following:

- **Infusion related reactions** including CRS are a known, common side-effect of rituximab treatment and are an expected side effect of BI-1206 treatment. Symptoms could include rash, fever, rigors, bronchospasm, and hypotension. All patients will receive supportive care including pre-medication (see Section 5.9.2) and will be monitored before during and after infusion.

- **Side effects resulting from lymphodepletion and/or depletion of immune effector cells**, notably infections related to neutropenia and/or lymphopenia. Neutropenia is considered unlikely based upon the results of preclinical studies undertaken in two murine models that expressed hCD32b and hCD20 under the control of human promoters and on a mCD32b null background. These models demonstrated that BI-1206 ± rituximab selectively depleted B cells preferentially to other lymphoid or myeloid lineage cells. In the event these AE do manifest it is anticipated they will be readily manageable in the context of advanced B-cell malignancies. Haematology assessments conducted during the trial will include assessment of white blood cells (WBC) with differential count (eosinophils, basophils, neutrophils and lymphocytes) and B cell levels. Furthermore, patients who are Hepatitis (Hep) B, C or Human Immunodeficiency Virus (HIV) positive, or who have an active, ongoing infection or an active, known or suspected autoimmune disease will not be eligible for trial participation.

- **Effects on blood pressure,** Blockade of CD32b by BI-1206 could theoretically lead to treatment related changes in blood pressure. Blood pressure will be regularly monitored during the course of the trial and will be managed as required in line with local practice.

- **Thrombocytopenia/platelet count decreased.**
  Included due to reported clinical data for the CRUKD/16/001 study. Laboratory test results are regularly monitored during the course of the trial and will be managed in line with local practice. Please see current version of IB for rate of occurrence.

- **Elevated transaminases.**
  Included due to reported clinical data for the CRUKD/16/001 study. Laboratory test results are regularly monitored during the course of the trial and will be managed in line with local practice. Please see current version of IB for rate of occurrence.

- **Ocular toxicity** BI-1206 binding to the eye or spinal cord is unlikely given the limited potential that antibodies have to cross the blood brain barrier. However given their, albeit remote, potential to occur eye examinations have been included in the schedule of events to allow for assessment throughout study treatment. See Section 5.9.3 .
- **Tumour-lysis syndrome (TLS)** is a known, side effect of mAb therapy. Patients will be risk-assessed for TLS and receive supportive care as described in Section 5.9.1
- **Autoimmune disease.** From the observational studies in a murine CD32b$^{-/-}$ transgenic model it has also been noted that CD32b inhibition is tolerated but there are certain, as yet unelucidated, genetic factors that can give rise to a profound autoimmune state in susceptible animals. The relevance of these factors to the proposed trial is expected to be limited by virtue of the short duration of CD32b inhibition by BI-1206 in vivo as compared to the life-long and total absence of CD32b in CD32b-/- mice. Patients with active autoimmune disease (as defined in the protocol) will be excluded from the trial. Autoimmune assessments will be performed as clinically indicated.

- **Potential for an anti-drug antibody (ADA) response.** Despite the reported occurrence of MAHA in the murine toxicology studies the potential for neutralising antibodies directed against BI-1206 in trial patients is expected to be minimal by virtue of the fact that BI-1206 is a fully human antibody. Experience with other approved humanised therapeutic antibodies suggest an incidence of ADA ranging from <1% to over 30% [39, 40]. Neither the frequency nor the impact of these ADA (if observed) on the efficacy or tolerability of BI-1206 can be predicted ahead of the trial but will be monitored during the trial.

- **Combination effects.** The undesirable effects of rituximab are generally manageable when used as monotherapy or in combination with cytotoxic chemotherapy. In combination with BI 1206 these effects may be present and could be exacerbated. Patients will be monitored closely for exacerbation of known or suspected toxicities and for unexpected combination adverse effects

2.3 Rationale for the proposed trial

For the majority of patients, B-cell NHL and CLL are incurable using existing therapeutic approaches. Although anti-CD20 directed therapy has improved outcomes, very many patients still relapse following treatment or are refractory to it and therefore additional novel non-cross resistant therapies are required.

The human CD20 mAb rituximab was the first mAb approved for cancer immunotherapy, and has been widely administered to patients with B-cell cancers including FL, DLBCL, CLL and MCL [41] in addition to an expanding number of autoimmune conditions. While rituximab is efficacious in FL and DLBCL, improving overall survival, only modest responses are seen in CLL and MCL. Furthermore, even in rituximab-responsive lymphoma sub-types some individuals show initial resistance or subsequently develop it.

BI-1206 is a fully-human anti-CD32b (FcγRIIB) antagonistic antibody that, in addition to directly killing tumour cells, is thought to work by prolonging anti-CD20 antibody residence on the cell membrane of cancer cells, preventing them from becoming resistant to treatments such as rituximab. It is anticipated that BI-1206 will have appreciable single agent activity but that the main likely clinical use will be in combination with rituximab and other sensitive antibodies preventing their internalisation by FcγRIIB and thereby augmenting their activity. Consequently, the clinical trial has been designed to allow

evaluation of the tolerability of BI-1206 as a single agent but also to partner BI-1206 with an anti-CD20 antibody at the earliest possible opportunity. Rituximab has been chosen as the most appropriate anti-CD20 antibody for use in combination at the start of this trial (see Section 2.2.6).

To evaluate these two possible modes of action, BI-1206 will be examined as a monotherapy in Arm 1, and concurrent administration of BI-1206/rituximab will be investigated in Arm 2 in both Parts A and B of the trial.

In the CRUKD/16/001 clinical trial, dose escalation phase (Part A), CD32b expression will be measured for information only; results will not be used as part of the eligibility criteria. The primary endpoints for this phase of the trial are safety and tolerability. CD32b expression will therefore be captured during study screening assessments to permit retrospective correlation of CD32b status (positive or negative) with the frequency and nature of any BI-1206 related toxicities, to further clarify the mechanistic pharmacology of CD32b inhibition.

The expansion phase (Part B), will be an expansion cohort of selected patients expressing the CD32b target and therefore form part of the eligibility criteria. Data from samples analysed from treated patients in Part A will be used to refine pre-screening selection requirements for Part B.

2.3.1 Rationale for BI-1206 starting dose

[redacted]

[redacted]

A starting dose of 0.4 mg provides a safety margin of more than 3,000-fold in relation to the GLP toxicology study and a 10-fold margin of safety over the ED_{10} value established in the in vivo PKPD study. BI-1206 has been shown to have no agonistic activity and at low doses BI-1206 is likely to undergo rapid clearance due to target mediated drug disposition. Therefore the selected starting dose is believed to be justifiable based on the large multiple of safety it offers over the animal studies; receptor occupancy not being sufficiently high to impede physiological function and B cell depletion being minimised by virtue of rapid clearance of the drug product at low doses.

3 TRIAL DESIGN

3.1 Clinical trial objectives and endpoints

3.1.1 Primary objectives and endpoints

Primary objectives	Endpoints
Part A Escalation phase	
Arm 1: To propose a recommended dose for Phase II evaluation of BI-1206 as a single agent in by:	
(a) Establishing the maximum tolerated dose (MTD) or maximum administered dose (MAD) of BI-1206 given once weekly for four weeks, via intravenous infusion in patients with relapsed or refractory B-cell malignancies in Part A only.	(a) Determining the maximal dose (up to 800 mg) of BI-1206 at which no more than one patient out of up to six patients at the same dose level experience a highly probably or probably BI-1206 related dose-limiting toxicity during induction therapy and up to one week post the fourth infusion.
(b) Assessing the safety and toxicity profile of BI-1206 as a single agent in Part A and Part B	(b) Documenting adverse events (AEs), serious adverse events (SAEs) (graded according to NCI- CTCAE Version 4.02) and laboratory parameters and determining their causality in relation to BI-1206. Causality of AEs/SAEs will be assessed by the Investigator.
Arm 2: To propose a recommended dose for Phase II evaluation of BI-1206 in combination with an anti-CD20 antibody by:	
(c) Establishing the MTD or maximum administered dose MAD of BI-1206 and an anti-CD20 antibody given once weekly for four weeks, via intravenous infusion in patients with relapsed or refractory B-cell malignancies in Part A only.	(c) Determining the maximal dose (up to 800 mg) of BI-1206 at which no more than one patient out of up to six patients at the same dose level experience a highly probably or probably BI-1206 or anti-CD20 antibody-related dose-limiting toxicity during induction therapy and up to one week post the fourth infusion.
(d) Assessing the safety and toxicity profile of BI-1206 in combination with an anti-CD20 antibody in Part A and B.	(d) Documenting AEs, SAEs (graded according to NCI-CTCAE Version 4.02) and laboratory parameters and determining their causality in relation to BI-1206 and, where appropriate, anti-CD20 antibody. Causality of AEs/SAEs will be assessed by the Investigator.
Part B Expansion phase	
Assessing the safety and toxicity profile of: • BI-1206 as a single agent in Arm 1 at the RP2D as determined in Part A (Part B, Arm 1) • BI-1206 when given in combination with an anti-CD20 monoclonal at the RP2D combination dose as determined in Part A (Part B, Arm 2)	Documenting AEs, SAEs (graded according to NCI-CTCAE Version 4.02) and laboratory parameters and determining their causality in relation to BI-1206 and, where appropriate, anti-CD20 antibody. Causality of AEs/SAEs will be assessed by the Investigator.

3.1.2 Secondary objectives and endpoints

Secondary objectives	Endpoints
Parts A and B	
To determine the PK profile of BI-1206 (± an anti-CD20 mAb) as a single agent in patients with relapsed or refractory B cell malignancies.	Measurement of PK parameter values for BI-1206 (as a single agent and when given in combination with an anti-CD20 monoclonal antibody) during the BI-1206 treatment period including AUC, C_{max}, T_{max}, and half-life ($T_{½}$) in serum samples using enzyme-linked immunosorbent assay (ELISA).
To assess the immunogenicity of BI-1206 (± an anti-CD20 mAb) in patients with relapsed or refractory B cell malignancies.	Measurement of anti-drug antibody (ADA) response to BI-1206 (as a single agent and when given in combination with an anti-CD20 mAb) during the BI-1206 treatment period using ELISA.
To evaluate the effect of BI-1206 (± an anti-CD20 mAb) on the depletion of peripheral blood B cells (B lymphocytes).	Measurement of peripheral blood B-lymphocyte depletion during the BI-1206 treatment period (as a single agent and when given in combination with an anti-CD20 mAb) using flow cytometry.
To document possible anti-tumour activity of BI-1206 (± an anti-CD20 mAb) in patients	Assessment of best disease response according to the revised response criteria for malignant lymphoma (Cheson, 2014) Waldenström macroglobulinaemia assessment criteria (Owen 2013, Kimby 2006) or NCI chronic lymphocytic leukaemia (CLL) criteria (Hallek, 2008).
To measure the duration of response to BI-1206 (± an anti-CD20 monoclonal antibody) over a follow-up period of 1 year.	Measure progression free survival (PFS) and overall survival (OS) at 1 year after the first BI-1206 administration on the study for all patients.

3.1.3 Tertiary objectives and endpoints

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

3.2 Design of the clinical trial

This is a multicentre, first in human (FIH), open label dose escalation trial, Phase I/IIa study in patients with B-cell malignancies. The clinical trial is in two parts (see Figure 2);

Part A: The first part of the study will be a dose escalation stage conducted in two arms:

- **Arm 1 (single agent):** Dose escalation phase to determine the MTD or MAD and recommended Phase II dose (RP2D) for evaluation of BI-1206 as a single agent.

- **Arm 2 (combination):** Dose escalation phase to determine the MTD or MAD and RP2D of BI-1206 administered in combination with an anti-CD20 antibody. Rituximab has been chosen as the most appropriate anti-CD20 antibody (see Sections 2.2.6 and 2.2.7).

Part B: The second part of the study will be a dose expansion stage conducted in two arms:

- **Arm 1 (single agent):** Expansion cohort of up to 25 patients with CD32b+ B-cell malignancies administered single agent BI-1206 at the RP2D as determined in Part A, Arm 1. This expansion will include a minimum of 12 chronic lymphocytic leukaemia (CLL) and 6 mantle cell lymphoma (MCL) patients.
  Part B, Arm 1 will be able to open once a RP2D in Part A Arm 1 is established.

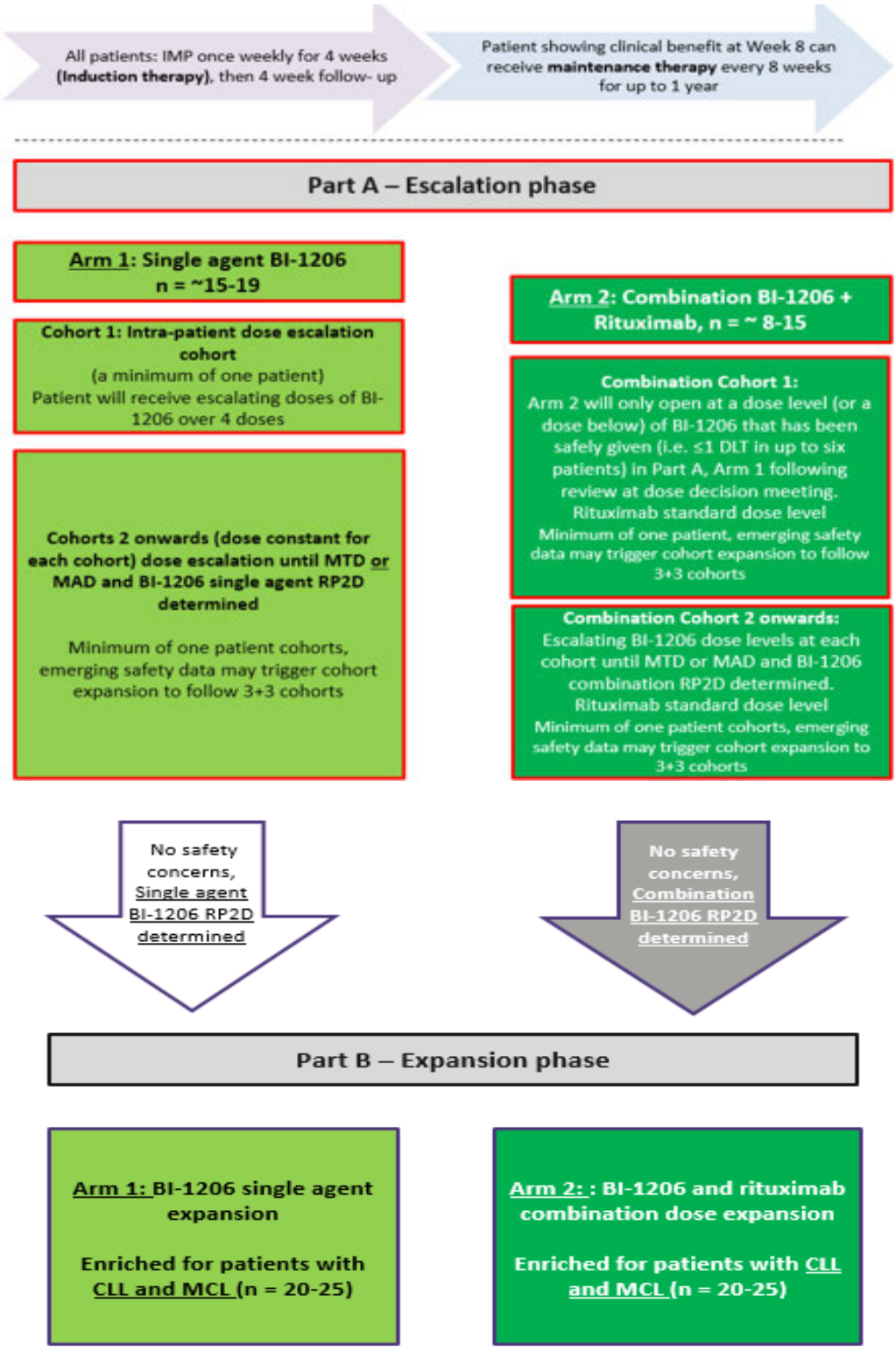
- **Arm 2 (combination)**: Expansion cohort of up to 25 patients with CD32b+ and CD20+ B-cell malignancies at the RP2D that can be given with an anti-CD20 antibody as determined in Part A. This expansion will include a minimum of 12 CLL and 6 MCL patients.
  Part B, Arm 2 will be able to open once a RP2D in Part A Arm 2 is established.

In both Parts A and B, if a patient shows evidence of clinical benefit (as defined in Section 10.2), they will be eligible to continue on maintenance therapy. Maintenance therapy will consist of a single dose of BI-1206 ± rituximab every eight weeks for up to one year after Week 1 of induction therapy.

It is expected that up to 81 evaluable patients will be required to complete this trial, with the final number depending on the number of dose levels explored.

Figure 2: Schematic of trial design

Boxes outlined in red are those to which the DLT definition described in Section 3.3 applies.



3.3 Definition of dose limiting toxicity

Some of the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) definitions are derived from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02. Please note that not all of the events described as DLTs are fully supported by NCI CTCAE but are formed by amalgams of different events in order to assist with assessments of adverse events.

The definition of DLT applies to both the single agent and combination dose escalation arms (Part A of the study [boxes outlined in red in Figure 2]).

A DLT is defined as a highly probably or probably **BI-1206 or rituximab-related AE occurring during** the four weeks of induction treatment and up to one week post the fourth infusion of BI-1206 (i.e. by Day 28/Week 5) which fulfils one or more of the following criteria:

- Neutropenia or neutrophil count decrease Grade 4 (ANC < 0.5 x 10^9/L) for >10 days duration *see note despite growth factor support
- Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) with Grade 3 or 4 neutropenia (absolute neutrophil count [ANC] <1.0 x 10^9/L) and fever ≥38.5ºC).
- Infection (documented clinically or microbiologically) with Grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L)
- Thrombocytopenia or platelet count decrease Grade 4: a) for ≥5 days*see note, or b) associated with active bleeding, or c) requiring platelet infusion
- Grade 3 or 4 non-haematological toxicity. This includes Grade 3 and 4 biochemical AEs as DLTs.

  EXCLUDING:

  - Grade 3 or 4 nausea or vomiting in patients who have not received optimal treatment with anti-emetics
  - Grade 3 or 4 diarrhoea in patients who have not received optimal treatment with anti-diarrhoeals
  - Alopecia
  - Grade 3 infusion related reactions
  - Transient, asymptomatic Grade 3 biochemical abnormalities if agreed by the Sponsor and the study team, including the Chief Investigator
- Event with a fatal outcome.

***Note: In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia, a full blood count must be performed at least on Day 10 (Day 5 for thrombocytopenia) 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. Please See Section 5.9.4 'Management of thrombocytopenia (Grade 4)' for further details.**

Refer to Section 5.3 for detail concerning intra-patient dose escalation and DLT.

DLTs defined above will be considered for the purposes of dose escalation decisions; however, should cumulative toxicity become apparent this will also be taken into consideration when determining either the next dose level or the RP2D

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

3.4 Definition of maximum tolerated dose

3.4.1 Part A, Arm 1:Single-agent dose escalation

If two out of up to six patients at the same dose level experience a DLT as defined in Section 3.3, this dose level of BI-1206 will be considered the maximum administered dose level (MAD) and no further patients will be treated at this dose level. In this case, the maximum tolerated dose (MTD) will be determined as a dose level below the MAD, which could be a dose previously administered or an intermediate dose between a dose already administered and the MAD. This MTD will be agreed following the review of all the relevant toxicity data between the Sponsor and the study team, including the Chief Investigator.

The MAD could also equal the MTD in the event that dose escalation is stopped before two DLTs are observed at a given dose level due to the expectation that higher dose levels would be too toxic to administer to patients, or if the 800 mg dose level is reached.

The RP2D in Part A, Arm 1 which will be used in Part B, Arm 1 of the clinical trial, will be determined by the Sponsor, Chief Investigator and Principal Investigators, following review of all relevant pharmacokinetic/pharmacodynamic (PK/PD) and clinically relevant toxicity data for all patients entered onto the trial in Part A Arm 1, and the identified MTD or MAD. All significant toxicities and available data from Part A, Arm 2 and data from any other trials investigating BI-1206 will also be considered in the determination of the RP2D.

3.4.2 Part A, Arm 2: Combination dose escalation

The MTD and MAD of BI-1206, when given in combination with rituximab and will be defined as above (Section 3.4.1).

The MAD could also equal the MTD in the event that dose escalation is stopped before two DLTs are observed at a given dose level due to the expectation that higher dose levels would be too toxic to administer to patients, or if the 800 mg BI-1206 dose level is reached. The MTD and MAD of BI-1206 in combination with rituximab (at a fixed dose 375mg/m^2) may be different to that of the single agent BI-1206 in Part A, Arm 1.

The RP2D from Part A, Arm 2 which will be used in Part B (Arm 2) of the clinical trial, will be determined by the Sponsor, Chief Investigator and Principal Investigators, following review of all relevant PK/PD and clinically relevant toxicity data for all patients entered onto the trial in Part A Arm 2, and the identified MTD or MAD. All significant toxicities and available data from the Part A Arm 1 and data from any other trials investigating BI-1206 will also be considered in the determination of the RP2D.

3.5 Patient evaluability

3.5.1 Response

All patients who meet the eligibility criteria, receive at least one administration of mAb (BI-1206 with/without rituximab) as part of this trial, have a baseline assessment of disease and at least one repeat disease assessment will be evaluable for response.

3.5.2 Safety

All patients receiving at least one administration of mAb (BI-1206 with/without rituximab) as part of this trial will be evaluable for safety.

3.5.3 Single Agent Dose escalation decisions (Part A, Arm 1)

Patients treated during the Part A, Arm 1 dose escalation phase of the trial who either receive four administrations of BI-1206 or experience a DLT will be evaluable for dose escalation and/or cohort expansion decisions in Part A, Arm 1.

Patients who receive less than 80% of their total planned induction doses (total across the four administrations) but complete the DLT period (Week 5) are not evaluable for dose escalation decisions (unless they have experienced a DLT).

Data from all patients who receive less than 4 doses of BI-1206 (single agent) and any available data from Part A, Arm 2 (if opened) will also be reviewed and taken into consideration at dose decision meetings. Data from any other trials investigating BI-1206 will also be considered in the dose escalation decisions.

For patients who do not receive the total full dose, please see Section 6.2.5.6 for decision making on continuation of treatment. Section 5.9.6 'Dose delays/treatment discontinuation' also offers guidance for re-challenging patients post related AE observation.

3.5.4 Combination dose escalation decisions (Part A, Arm 2)

The starting dose for BI-1206 in Part A, Arm 2 will not exceed the highest dose of single agent of BI-1206 that has been safely administered in Part A, Arm 1 (at the time of opening Part A, Arm 2), and which is deemed clinically appropriate to combine with rituximab. The starting dose in Part A, Arm 2 will be determined at a dose decision meeting following review of a completed cohort in Part A, Arm 1.

Once Arm 2 is opened, patients treated in the combination dose escalation cohorts who either receive four administrations of BI-1206 in combination with rituximab or experience a DLT will be evaluable for dose escalation and/or cohort expansion decisions in Part A, Arm 2.

Patients who receive less than 80% of their total planned induction doses (total across the four administrations) but complete the DLT period (Week 5) are not evaluable for dose escalation decisions (unless they have experienced a DLT).

Data from all patients who receive less than 4 doses of BI-1206 in combination with rituximab and available data from Part A, Arm 1 will also be reviewed and taken into consideration for subsequent dose escalations in the combination arm. Data from any other trials investigating BI-1206 will also be considered in the dose escalation decisions.

For patients who do not receive the total full dose, please see Section 5.9.6 'Dose delays/treatment discontinuation' which also offers guidance on the thresholds for re-challenging patients post related AE observation.

3.5.5 Survival

All patients receiving at least one administration of mAb (BI-1206 with/without rituximab) as part of this trial will be evaluable for survival (OS and PFS) regardless of whether they subsequently receive other anti-cancer treatments. Please see Section 7.5.2.

3.6 Study duration

Following completion of recruitment to each escalation arm (single agent or combination) in Part A, the data will undergo review and assessment by the Sponsor. The Sponsor will confirm the decision to progress to Part B of trial and the respective expansion arm (Arm 1 single agent or Arm 2 combination) will open to recruitment. The single agent (Arm 1) and combination (Arm 2) expansion cohorts in Part B may open and progress independently of each other. The Sponsor will confirm when recruitment to each of the expansion cohort is complete.

The number of patients recruited to the dose escalation arms of the study could increase in the event that additional cohorts are required to investigate intermediate doses of BI-1206.

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. Written (signed and dated) informed consent and be capable of co-operating with treatment and follow-up.
2. B-cell lymphoma or chronic lymphocytic leukaemia proven by histology or flow cytometry, relapsed or refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient. Patients should have received at least one line of conventional previous therapy which must have included a rituximab based regimen.
3. Part B only: CD32b positive malignancy as demonstrated centrally by immunohistochemistry or flow cytometry prior to study entry.
4. Life expectancy of at least 12 weeks.
5. World Health Organisation (WHO) performance status of 0-2 (Appendix 1).
6. Haematological and biochemical indices within the ranges shown below to confirm patients eligibility. These measurements must also be performed within one week before their first dose of mAb (BI-1206 and/or rituximab) as part of this study.

Laboratory Test	Value required
Haemoglobin (Hb)	≥90 g/L (red cell support is permissible)
Absolute neutrophil count (ANC)	≥1.0 x 10^9/L (or >0.5 x 10^9/L if due to lymphoma), granulocyte - colony stimulating factor (G-CSF) support is not permissible at screening
Platelet count	≥50 x 10^9/L (or ≥30 x 10^9/L if due to malignant involvement of bone marrow)
Serum bilirubin Or: Alanine amino-transferase (ALT) and /or aspartate amino-transferase (AST)	≤1.5 x upper limit of normal (ULN) unless raised due to Gilbert's syndrome in which case up to 3xULN is permissible. ≤ 2.5 x (ULN) unless raised due to malignant hepatic involvement in which case up to 5 x ULN is permissible
Either: Calculated creatinine clearance (Cockcroft Gault) Or: Isotope clearance measurement	 ≥30 mL/min (uncorrected value) ≥30 mL/min (corrected)

7. 18 years or over.
8. B-cell lymphoma patients only: patients has at least one measurable lesion by CT scan (defined as greater than 1.5 cm in one axis) or in the case of Waldenström's macroglobulinemia, disease must be assessable by the criteria stated in Appendix 6.
9. **Patients recruited to Arm 2 in Parts A and B (combination arms) only:** CD20 positive malignancy as demonstrated by immunohistochemistry or flow cytometry prior to study entry.

4.1.2 Exclusion Criteria

1. Allogenic bone marrow transplant within 12 months prior to the first dose of BI-1206 or presence of chronic graft versus host disease.
2. Patients with clinically active leptomeningeal or central nervous system lymphoma/leukaemia.
3. Patients who receive doses of prednisolone >10 mg daily (or equipotent doses of other corticosteroids) are not eligible for the study unless administered as pre-medication.

   During the screening period, doses of up to 20 mg per day may be given but the dose must be reduced to 10 mg/day by Week 1 Day 1. See Sections 5.9.2 and Section 5.10 regarding allowable pre-medication and conditions for steroid use
4. Known or suspected hypersensitivity to study drugs.
5. Cardiac or renal amyloid light-chain (AL) amyloidosis.
6. Patients who have received radiotherapy, endocrine therapy*, immunotherapy, chemotherapy or investigational medicinal products during the previous 4 weeks before treatment, must discuss with the CI and Sponsor to agree the appropriate interval (if required) between prior therapy and commencement of BI-1206. The wash out duration will be compatible with the clinical context within which previous medication had been used. Patient must also have recovered from therapy related toxicity.

   * exceptions to endocrine therapy are noted in exclusion criteria #13 and #19.
7. Ongoing toxic manifestations of previous treatments. Exceptions to this are alopecia or certain ≤Grade 2 toxicities, which in the opinion of the Investigator and the Sponsor should not exclude the patient.
8. Ability to become pregnant (or already pregnant or lactating). However, those female 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[4], for four weeks before entering the trial, during the trial and for twelve months after completing treatment are considered eligible.
9. 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 BI-1206 or rituximab on the study, throughout the trial and for twelve 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[4]). Men with pregnant or lactating partners should be advised to use barrier method contraception (e.g. condom plus spermicidal gel) to prevent exposure to the foetus or neonate.
10. Major thoracic or abdominal surgery from which the patient has not yet recovered.
11. At high medical risk because of non-malignant systemic disease including infection.
12. Known to be serologically positive for hepatitis B, hepatitis C (hepatitis C antibody positive patients are eligible providing PCR for viral RNA is negative) or human immunodeficiency virus (HIV).

[4] 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.

13. Patients with an active[5] autoimmune disease (not including CLL auto-immune disease). Patients with Type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger will be permitted to participate.

14. Concurrent congestive heart failure, prior history of class III/ IV cardiac disease (New York Heart Association [NYHA] Section 16.3 Appendix 3), history of clinically significant cardiac ischaemia or clinically significant history of cardiac arrhythmia in the past 6 months.

    For events that are deemed to be not clinically significant and have occurred in the last 6 months, Investigator must discuss with CI and Sponsor to confirm eligibility.

15. Patients for whom rituximab is contraindicated due to severe previous hypersensitivity or any other reason (Arm 2 in Parts A & B [combination arms] only).

16. Ongoing infection requiring treatment with antibiotics, antifungals or antivirals. Prophylactic use of antibiotics, antifungals or antivirals will not exclude patients.

17. Any other condition which in the Investigator's opinion would not make the patient a good candidate for the clinical trial.

18. Is a participant or plans to participate in another interventional clinical study, whilst taking part in this Phase I/IIa study of BI-1206. Participation in an observational study would be acceptable.

19. Current malignancies of other types, with the following exceptions:

    - Adequately treated cone-biopsied *in situ* carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin.

    - Asymptomatic prostate cancer without known metastatic disease, with no requirement for therapy or requiring only hormonal therapy (either past or continuing) and with normal prostate-specific antigen for $\geq$1 year prior to start of study therapy are eligible for the trial.

    - Current or prior malignancy which could affect compliance with the protocol or interpretation of results. Patients with curatively-treated non-melanoma skin cancer, non-muscle-invasive bladder cancer, or carcinomas-in-situ are generally eligible.

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.

Eligible patients must be enrolled in the electronic data capture (EDC) system by site staff and then registered by the CDD before they start treatment with BI-1206 ±rituximab. Eligible patients will be allocated a study number by the EDC system during the enrolment process. The CDD will send confirmation of the patient registration, including the assigned dose level and assigned treatment arm (single agent or combination), to the Investigator following enrolment of the patient. Study treatment may only be administered after this confirmation has been received.

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[5] History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone will be eligible as will be patients with controlled Type I diabetes mellitus on a stable dose of insulin). Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

• Rash must cover < 10% of body surface area

• Disease is well controlled at baseline and requires only low-potency topical corticosteroids

• No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

5 TREATMENT

5.1 Selection of the Phase I starting dose and schedule

5.1.1 Rationale for starting dose BI-1206 and rituximab

BI-1206 (single agent) will be given at a starting dose of 0.4 mg, please refer to Section 2.3.1 for rationale.

The BI-1206 dose levels are flat doses given in units of mg for each cohort, whereas the rituximab doses are adjusted for the body surface area (BSA) of each patient and given in units of mg/m^2.

The dose(s) of rituximab used in Part A & B of the study will be a fixed dose of 375 mg/m^2 based upon the approved dose of rituximab.

For the purpose of this trial, all patients including CLL will receive 375 mg/m^2 for every rituximab infusion for consistency. The proposed weekly dosing schedule with BI-1206 and rituximab is in line with the rituximab SmPC standard of care for patients who receive rituximab alone. The 8 weekly maintenance therapy schedule is at a frequency in line with rituximab administration post chemotherapy and will only be given if patients are showing clinical benefit as defined in Section 10.2.

Single agent BI-1206 (Arm 1) will be initiated first in Part A and BI-1206 in combination with rituximab (Arm 2) may start once the intrapatient dose escalation cohort (Cohort 1) in Arm 1 has been completed.

The starting dose level for BI-1206 in Part A, Arm 2 will not exceed the highest dose of BI-1206 that has been safely given as a single agent in Part A, Arm 1 and deemed safe to be given in combination, following review in the Dose Decision Meeting (see Section 5.3). This will allow assesment of any single agent BI-1206 toxicity at the specified dose level to decide if it would be clinically appropriate to start the combination arm (Part A, Arm 2)

Once the combination dose escalation arm (Arm 2) is opened, both arms will run in parallel but independently, to determine RP2D of single agent BI-1206 in Part A, Arm 1 and RP2D of BI-1206 in combination with rituximab in Part A, Arm 2 (see Sections 5.4 and 5.5).

The RP2D of BI-1206 in the relevant arm (single agent or combination) needs to be established in Part A before the respective expansion cohort in Part B of the trial opens to recruitment (single agent expansion cohort, Arm 1 and combination expansion cohort, Arm 2, see Sections 5.7 and 5.8). Arm 1 and Arm 2 in Part B may open and progress independently of each other.

5.2 Dosing schedule/treatment schedule

5.2.1 Dosing schedule/treatment schedule in BI-1206 single agent escalation phase (Part A, Arm 1)

BI-1206 will be administered once weekly for four weeks, this will be classified as induction therapy. The starting dose of BI-1206 will be 0.4 mg given as a 30 minute (min) intravenous (IV) infusion. Intra-patient dose escalation will be performed in the first cohort which will consist of a minimum of one patient. In Cohort 1, if a patient withdraws before completing induction therapy for reasons other than DLT they will be replaced, following a dose review meeting at which the planned dose level for the replacement patient will be decided (the starting dose for this patient will be at or below a level already received on the study, see Section 5.4).

Subsequent cohorts will be at doses that are approximately comparable to or above the expected pharmacologically active dose (PAD) determined based on the preclinical toxicology data (>60 mg). These cohorts will include a minimum of one patient cohorts as described in Section 5.4. The maximum weekly dose of BI-1206 to be administered will be 800 mg, infusion times will vary dependent on the

dose administered. Patients with clinical benefit at eight weeks (as defined in Section 10.2) will move to a maintenance phase of treatment. Refer to Section 5.2.5.

5.2.2 Dosing schedule/treatment schedule in BI-1206/rituximab combination escalation phase (Part A, Arm 2)

BI-1206 and rituximab will each be administered once weekly for four weeks via separate IV infusions. Based on the proposed mechanism of action of BI-1206 binding to the CD32b receptor and blocking its ability to internalise rituximab, BI-1206 will be administered prior to rituximab. The timeframe within which the two infusions can be given (i.e. on the same day or on subsequent days) will be determined by the length of each infusion. At Week 1 both infusions will be administered over a longer period of time as a precautionary measure and so the BI-1206 dose will be given on Day 1 and the rituximab dose on Day 2. In subsequent weeks, if patients have not experienced a significant infusion reaction at Week 1 then the BI-1206 and rituximab infusions can be given at a faster rate. Therefore, from Week 2 onwards, if the infusion times allow, the doses of BI-1206 and rituximab may be given on the same day. BI-1206 will be given prior to rituximab on all occasions. If infusion times are not compatible with same-day dosing, administration of BI-1206 and rituximab on subsequent days will continue. These cohorts will include a minimum of one patient as described in Section 5.5.

Patients who show clinical benefit at eight weeks (as defined in Section 10.2) will move to a maintenance phase of treatment (refer to Section 5.2.5).

Figure 3: Combination dosing schedule during induction therapy

	Week 1				Week 2				Week 3				Week 4			
	D1	D2	D3	D4	D8	D9	D10	D11	D15	D16	D17	D18	D22	D23	D24	D25
BI-1206	X				X				X				X			
Rituximab		X			X[1]				X[1]				X[1]			

[1] Rituximab may be given on Day 1 following BI-1206 from Week 2 onwards if no significant infusion reaction has been observed at Week 1 and if infusion times allow this.

Otherwise it will be given on Day 2 as in Week 1.

5.2.3 Dosing schedule/treatment schedule in BI-1206 single agent expansion phase (Part B, Arm 1)

BI-1206 will be administered once weekly for four weeks via IV infusion at the RP2D as defined by Part A, Arm 1 this will be classified as induction therapy; refer to Section 5.7. Patients with clinical benefit (as defined in Section 10.2) at eight weeks will move to a maintenance phase of treatment as described in Section 5.2.5.

5.2.4 Dosing schedule/treatment schedule in BI-1206/rituximab combination expansion phase (Part B, Arm 2)

BI-1206 and rituximab will each be administered once weekly for four weeks via separate IV infusions. BI-1206 will be administrated at the RP2D as defined in Part A, Arm 2 and rituximab at the fixed dose of 375 mg/m^2; this will be classified as induction therapy, refer to Section 5.8. Patients with clinical benefit (as defined in Section 10.2) at eight weeks will move to a maintenance phase of treatment as described in Section 5.2.5.

5.2.5 Dosing schedule/treatment schedule, maintenance therapy (Part A and Part B)

For all patients completing induction therapy in Parts A and B, and who are deriving clinical benefit at Week 8 (as defined in Section 10.2), maintenance therapy may be given. A patient's maintenance therapy will be the same as their induction therapy and will be given every eight weeks for up to one year after their first BI-1206 dose on the study (Week 1 of induction therapy).

- For patients in Arm 1 in Parts A and B (single agent arms) who continue on maintenance therapy, the dose of BI-1206 will be continued at the level of the last dose received in their induction therapy.
- For those patients in Arm 2 in Parts A and B (combination arms) who continue on maintenance therapy, these patients will continue to receive BI-1206 and rituximab at the level of the last dose received in their induction therapy.

5.3 Communication Plan where dose escalation (Part A) is to occur

5.3.1 Organisation and preparation for dose decision meetings.

Dose decision meetings will be organised by the Sponsor for weekly review of patient data during the first three weeks of the intra-patient dose escalation cohort in Arm 1 only, and subsequently during or following Week 5 of the last patient recruited to each cohort in Arm 1 or in Arm 2. Dose decision meetings will be triggered and occur independently for each treatment arm.

Required attendees/functional groups are as defined in the Sponsor's SOP: Sponsor Pharmacovigilance (PV) representative, Sponsor Medical Sciences representative (MS), Sponsor Clinical Study Manager or appropriate delegate, CI and PIs with patients at their sites undergoing review (a nominated sub- or co-investigator may attend in the PI's place if necessary). Optional attendees are Research Nurses or other relevant site staff and the following Sponsor representatives; Clinical Research Associates (CRAs), Clinical Study Co-ordinator (CSC), Clinical Data Manager (CDM) and, Project Leader (PL). PI's who do not have patients in the cohort under review are encouraged to attend but not required.

Prior to the dose decision meeting, the Sponsor will distribute the agenda and all necessary data to the meeting attendees and all study PIs if they are not available to attend the meeting, specifying which patients and data will form part of the review. The essential data to be reviewed to make decisions concerning changes in dose will be defined in the monitoring guidelines for the study. These will consist primarily of clinical data listings from Data Management (DM), safety data listings from PV and available pharmacokinetic and pharmacodynamic (PK/PD) assay data.

For intra-patient dose escalation, in order to ensure that the most recent trial data is under review data listings will be reviewed alongside anonymised safety data signed off by the site Investigator and faxed or emailed from site directly.

The dose decision for treatment of subsequent patients will be based upon safety data from all patients in a cohort after the last patient in the existing cohort completes their induction therapy and has been followed up for a minimum of 7 days following their fourth dose. Data from any previous cohorts in the same arm and data from complete/incomplete cohorts in the other arm will also be taken into account in dose decision meetings. Any available data from any other trials investigating BI-1206 will also be considered in the dose decision meetings.

5.3.2 Areas to be discussed at dose decision meetings.

Areas which should be discussed at the dose decision meeting include:

- Outline any relevant criteria specified by the protocol relating to changes in dose levels to the attendees e.g. study dose escalation scheme, dose limiting toxicity (DLT) criteria, criteria for expansion of cohorts (including any ≥Grade 2 related toxicity considered to be clinically relevant as defined in Section 5.4.2) etc. Patients treated since the last dose review meeting including IMP related adverse events noted and duration of treatment.

- Assessment and agreement on any dose limiting toxicities that may have occurred and resulting actions.
- Relevant PK and/or PD data available since the last dose decision meeting and any proposals to amend PK/PD scheduling based on emerging data (Section 8). In event of any changes to the sampling schedule, it should be noted the total blood volume and burden of the patient will not increase.
- Any available data from any other trials investigating BI-1206.
- Any additional relevant information relating to adverse events or patient safety which may have arisen following distribution of listings for the meeting and will therefore not be documented in the listings.
- Any possible concern after the review of cumulative data.
- Assessment and agreement on the appropriate next dose level or other action such as dose expansion, dose reduction or halt to recruitment.
- If the next cohort should be a minimum of one patient cohort or 3+3 cohort based on the emerging safety data.
- If it is appropriate to open the combination arm (Arm 2) and agreement of starting dose and size of cohort for the first cohort based on available data from Arm 1.

5.3.3 Follow-up of dose decision meetings

Following the meeting the Sponsor will prepare and disseminate minutes documenting the data reviewed per patient and any outcomes or decisions made. Dose limiting toxicities, SAEs, medically important events (as specified by the protocol) and suspected unexpected serious adverse reactions (SUSARs) discussed will be documented in the minutes and listed by patient. If changes to these emerge as part of the review and discussion the minutes will reflect these and any actions to be taken as a result. Dose decision meeting minutes will be distributed by the Sponsor to the CI, all study PIs and any other relevant site staff.

If due to exceptional circumstances, the CI is not able to attend the dose review meeting, the meeting minutes will be sent to the CI by email who will respond to confirm agreement with the dose decision and cohort size prior to recruitment of the next patient to the relevant cohort.
The outcome of the dose review will also be approved by the Sponsor's Head of Medical Sciences before recruitment of the next patient to the relevant cohort. Patients can only be registered and treated on the study following email confirmation from the Sponsor to the site of the agreed dose level and assigned treatment arm (single agent or combination) for the specific patient.

5.3.4 Dissemination of Safety data between dose decision meetings

Safety information relating to SUSARs will be collected and provided to the MHRA and Ethics Committee as outlined in Section 9. Where the Sponsor becomes aware of significant relevant safety information (such as a DLT or clinicially relevant ≥Grade 2 related toxicity to expand a cohort from a minimum of one patient to 3+3 cohorts) during treatment of patients on the study, this will be communicated to all PIs and relevant site staff by email as soon as is reasonably possible. Updates regarding the DLT assessment and actions to be taken will also be provided by email where needed with follow-up phone-calls where required.

5.4 BI-1206 single agent dose escalation scheme (Part A, Arm 1)

The weekly doses to be administered to each cohort are shown below (Table 1). Intermediate doses may be examined, e.g. a dose between 400 mg and 800 mg could be chosen for further investigation based on a review of the emerging safety data but in any event, dose increases will not exceed those described below. Intermediate dose levels will only be explored if deemed clinically appropriate after review of a completed cohort in Arm 1 and agreed in a dose decision meeting (see Section 5.3). The maximum weekly dose to be administered will be 800 mg.

An accelerated dose escalation scheme will be used in the initial dose levels which will occur in a minimum of one patient. Intra-patient dose escalation will be permitted until either a DLT is reported or the dose reaches 100 mg, which is above the expected PAD determined based on the preclinical toxicology data (>60 mg).

Please refer to Section 5.3 for details of the communication plan and process for dose escalation review and dissemination of information. In Cohort 1, if a patient withdraws before completing induction therapy for reasons other than DLT they will be replaced, following a dose review meeting with the Sponsor and CI at which the planned dose level for the replacement patient will be decided. The replacement patient would start treatment at a dose level that the previous patient has already received and the dose level at subsequent weeks would increase to a maximum of 50 mg in line with the dose escalations described in Table 1, so they may receive a dose of 50 mg for more than one week.

The decision to dose escalate between cohorts will be based on the four weeks (one week after the Induction Therapy Week 4 dose) safety data from patients in the current cohort and all available safety data from previous cohorts.

Table 1: Proposed single agent dose escalation schedule (subject to revision based upon emerging safety data; Part A, Arm 1)

Cohort Number	Total BI-1206 Dose (mg)	Cohort size[b]	Notes
1 (pt1 wk 1)	0.4	1	[redacted]
1 (pt1 wk 2)	2		[redacted]
1 (pt1 wk 3)	10		[redacted]
1 (pt1 wk 4)	50		[redacted]
Assess patient for safety for 7 days post Week 4 infusion before next cohort or before each patient if Cohort 1 consists of more than one patient			
Follow the last patient for safety in each cohort to 7 days post Week 4 infusion before the next cohort is opened to recruitment (all cohorts going forward)			
2	100	1[a] - 3	[redacted]
3	200	1[a] - 3	[redacted]
4	400	1[a] - 3	[redacted]
5	800	3 + 3	[redacted]

[a] Assumes that no clinically relevant ≥Grade 2 related toxcity has occurred

[b]Assumes that no DLTs are encountered and is also dependant on number of patients that need to be replaced (if patient withdraws for reasons other than DLT).

[redacted]

5.4.1 Action if DLT observed in Cohort 1 (0.4mg to 50 mg), Part A Arm 1

Cohort 1 will consist of a minimum of a single patient, with intra patient dose escalation permitted up to a maximum weekly dose of 50 mg. Safety data will be reviewed on a weekly basis prior to the next planned dose and a decision to dose-escalate will be made based on this data.

If a DLT is observed at or below a dose of 50 mg the cohort will be expanded to up to six patients at the dose level at which the DLT is first identified (the most recent dose prior to onset of the event identified as a DLT). If one out of the six patients experiences DLT, intra-patient dose escalation will cease but standard dose escalation will continue; subsequent cohorts will be expanded to three patients. If two or more out of the six patients experiences a DLT, decisions about future patients will be made in accordance with Figure 4.

5.4.2 Dose escalation and action if clinically relevant ≥Grade 2 related toxicity observed at dose levels from Cohort 2 onwards, Part A Arm 1

From Cohort 2 onwards, all cohorts will include a minimum of one patient (see Figure 4)

- In the first patient recruited, any episode of clinically relevant ≥Grade 2 related toxicity would trigger cohort expansion to a minimum of 3 patients.

- Clinical relevance of the related toxicity will be determined by review and agreement between the relevant Investigator, Chief Investigator and Sponsor according to the following definition:

  The test of clinical relevance is that the adverse event in question would cause the Investigator to re-evaluate the risk-benefit assessment of continuing therapy for the patient experiencing the event and to conclude that on a balance of probabilities, the risk-benefit ratio could be materially worsening

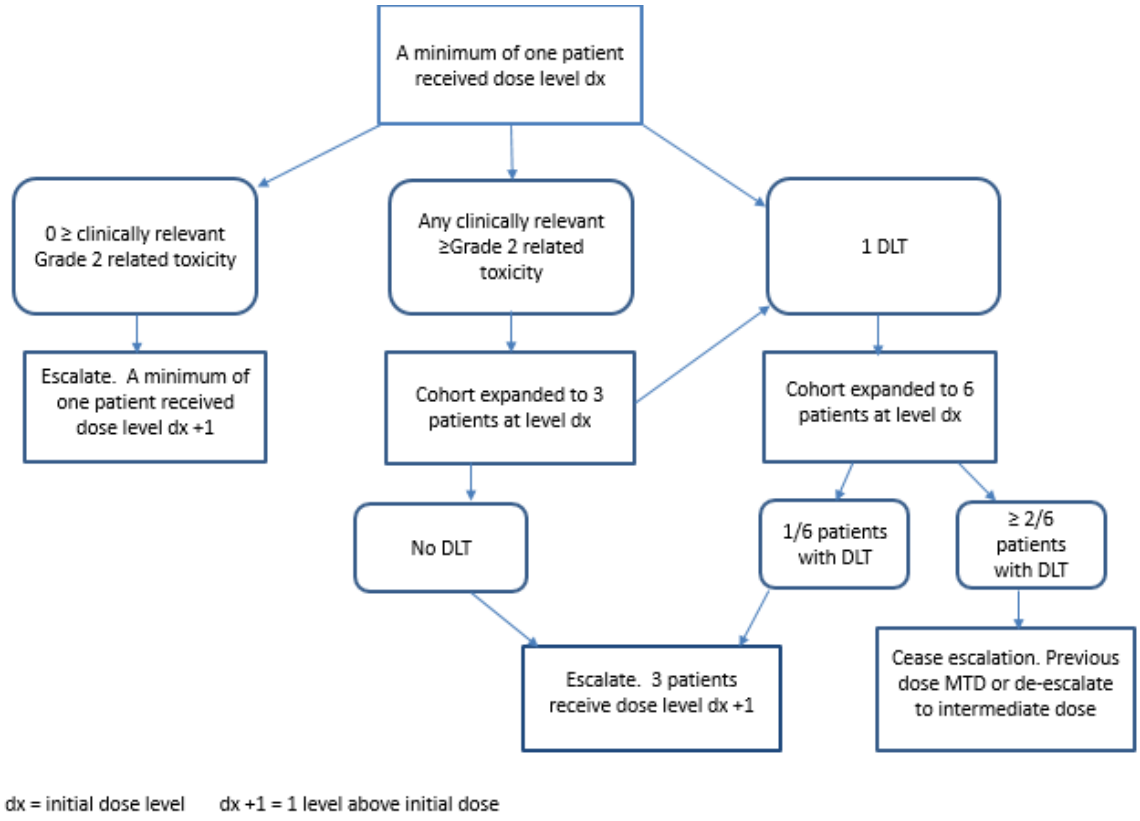
- The decision to expand a minimum of one patient cohort to a 3+3 cohort following a clinically relevant ≥Grade 2 related toxicity will be documented and distributed by the Sponsor to all Investigators as per Section 5.3.4. The decision may occur outside the dose decision meetings as it is dependent on when the event/s occurs. The assessment of a clinically relevant toxicity will end at Week 5 (same as the DLT period i.e.one week post fourth infusion).

- As per Section 9.4, related toxicity will be highly probably, probably and possibly related to BI-1206 (or rituximab in Arm 2).

It should be noted that dose escalation and cohort size decisions will be made based on data from completed cohorts in the single agent arm (Arm 1); available data from the combination arm (Arm 2) will be also be reviewed and considered in the Arm 1 dose decision meetings. Please refer to Section 5.3 for details of the communication plan, the process for dose escalation review and decision making and the dissemination of information.

All patients in a cohort must have completed induction therapy and 7 days post the fourth infusion for dose-escalation to the next cohort to occur. The second patient in any cohort will not commence treatment until after the first patient in that cohort has completed two infusions of BI-1206; the third patient in any cohort will not commence treatment until after the second patient in that cohort has completed one infusion of BI-1206.

Figure 4: Dose escalation decision-making and action if clinically relevant ≥Grade 2 related toxicity and/ or DLT observed at dose levels from Cohort 2 (Part A, Arm 1)



5.4.3 Dose escalation and action if a DLT observed at dose levels from Cohort 2 onwards, Part A, Arm 1

If one instance of DLT is observed in any cohort, the cohort will be expanded to include up to six patients. If one out of the six patients experience a DLT then dose escalation will continue, and the next cohort will consist of a minimum of 3 patients as decribed in Figure 4. If no DLTs are seen in 3 patients, further escalations will continue as 3+3 cohorts.

No additional patients will be added to a cohort after a second DLT is observed. Should DLT occur in more than two out of three or two out of six patients in a cohort, the previous dose level may not be the most appropriate RP2D. Intermediate dose levels may be explored if deemed clinically appropriate after review of a completed cohort, see Section 3.4.

Please refer to Section 5.3 for details of the communication plan and process for dose escalation review and dissemination of information. The proposed dose escalation scheme in Table 1 may be modified in light of emerging safety data following consultation between the Sponsor and the CI.

5.5 BI-1206 and rituximab escalation cohorts (Part A, Arm 2)

The combination escalation arm (Part A, Arm 2) will open to recruitment following review of a completed single agent dose level in Arm 1. The starting dose for BI-1206 in combination with rituximab will be agreed at a dose decision meeting based on data from completed cohorts in the single agent arm. The combination dose will not exceed the highest dose of BI-1206 safely given (≤1 DLT in up to six patients) as a single agent to date and must be deemed clinically appropriate to combine with rituximab.

The dose(s) of rituximab will be 375 mg/m^2 based upon the approved dose of rituximab. For the purpose of this trial, all patients including CLL patients will receive 375 mg/m^2 for every rituximab infusion for consistency.

Once the combination escalation arm (Part A, Arm 2) is opened, it will run in parallel to the single agent escalation arm (Part A, Arm1) but dose decisions and cohort size decisions will be made independently for each arm. Combination cohorts will also be a minimum of one patient and dose escalation/cohort expansion decision-making as described in Sections 5.4.2 and 5.4.3 will also apply to the combination escalation cohorts.

It should be noted that dose escalation decisions will be based on data from the combination arm (Arm 2) with available data from the single agent arm (Arm 1) and any other ongoing trials with BI-1206 also being reviewed and considered. Please refer to Section 5.3 for details of the communication plan and process for dose escalation review and dissemination of information.

All patients in a cohort must have completed induction therapy and 7 days post the fourth infusion without DLT for dose-escalation to the next cohort to occur. The second patient in any cohort will not commence treatment until after the first patient in that cohort has completed two infusions of BI-1206 in combination with rituximab; the third patient in any cohort will not commence treatment until after the second patient in that cohort has completed one infusion of BI-1206 and rituximab.

In Part A, Arm 2 the dose level of rituximab will be fixed and the dose level of BI-1206 will be explored in the escalation phase in order to establish the BI-1206 MAD or MTD and RP2D in combination with rituximab, see Section 3.4.

The BI-1206 doses explored in Part A, Arm 2 may follow the dose levels outlined in Table 1 but will be dependent on emerging data. Intermediate BI-1206 doses may be examined, e.g. a dose between 400 mg and 800 mg could be chosen for further investigation based on a review of the emerging safety data but in any event, dose increases will not exceed those described in Table 1. Intermediate dose levels will only be explored if deemed clinically appropriate after review of a completed cohort in Arm 2 and agreed in dose decision meeting (see Section 5.3).

The maximum weekly BI-1206 dose to be administered will be 800 mg in both Arm 1 and Arm 2.

5.6 Cohort expansion at maximum tolerated and/or maximum administered dose (Part A, Arm 1 and Arm 2)

Cohorts may be expanded to six patients as described in Sections 5.4.1 and 5.4.2. If only one out of six patients experiences a DLT, dose escalation will continue. If two out of up to six (i.e. between two and six) patients experience a DLT dose escalation will stop and this dose will be defined as the maximum administered dose (MAD). At least six patients will be treated at a dose below the MAD to define the MTD.

The MAD could also equal the MTD in the event that dose escalation is stopped before two DLTs are observed at a given dose level due to the expectation that higher dose levels would be too toxic to administer to patients, or if the 800 mg dose level is reached.

The single agent RP2D in Part B, Arm 1 of the proposed clinical trial will be determined by the Sponsor, CI and PIs, following review of all available PK/PD and clinically relevant toxicity data for all patients entered onto the trial in Part A (Arm 1 and Arm 2), and the identified MTD or MAD.

The combination RP2D in Part B, Arm 2 of the proposed clinical trial will be determined by the Sponsor, CI and PIs, following review of all available PK/PD and clinically relevant toxicity data for all patients entered onto the trial in Part A (Arm 1 and Arm 2), and the identified MTD or MAD.

Any available data from other trials investigating BI-1206 will also be considered in defining the RP2D in Arm 1 and Arm 2. The RP2D for each arm may be the same or different but it will not exceed 800 mg as per Table 1.

5.7 Single agent BI-1206 expansion cohort (Part B, Arm 1)

On determining the RP2D of single agent BI-1206 in Part A, Arm 1, up to 25 further patients will be enrolled into an expanded single agent cohort (Part B, Arm 1) at that dose level for further evaluation of toxicity and efficacy. This cohort will include a minimum of 12 chronic lymphocytic leukaemia (CLL) and six mantle cell lymphoma (MCL) patients.

5.8 BI-1206 and rituximab combination expansion cohort (Part B, Arm 2)

On determining the RP2D of BI-1206 in combination with rituximab in Part A, Arm 2, up to 25 further patients will be enrolled into an expanded combination cohort (Part B, Arm 2) at that dose level for further evaluation of toxicity and efficacy. This cohort will include a minimum of 12 CLL and six MCL patients.

5.9 Dose modifications

Protocol defined dose modification criteria for treatment in Part B will be reviewed and updated if required based on the emerging clinical data from Part A of the trial.

For the combination arms in Parts 1 and 2, BI-1206 and ritxumab should be administered independently of any dose delay to the other agent. The decision to continue with either agent alone, if the other has to be withdrawn, should be at the discretion of the investigator depending on whether there is clinical advantage to continuing with treatment.

5.9.1 Risk assessment for and management of tumour lysis syndrome

Prior to each infusion (BI-1206 or rituximab), patients should be risk assessed for tumour lysis syndrome (TLS) and treated with adequate hydration and administration of uricostatics starting 48 hours prior to the start of the infusion as well as prednisolone if appropriate. This may require a delay in the patient receiving treatment.

5.9.2 Management of infusion related reactions

Pre-medications as specified of oral paracetamol 1 gram and IV chlorphenamine 10 mg will be administered as standard at least 30 minutes prior to each BI-1206 or rituximab infusion. Hydrocortisone 100 mg IV or dexamethasone 8 mg IV may also be administered prior to administration of BI-1206 or rituximab infusion, at the same time as the chlorphenamine and paracetamol at the Investigator's discretion. Alternative premedication steroids, antihistamine and analgesics (painkillers) may be used if clinically indicated according to Investigator’s judgement, after discussion and approval from the CI and Sponsor.

Patients should be carefully monitored for signs of CRS or acute infusion reaction during each infusion, e.g. signs such as urticaria, wheeze, hypotension, tachycardia, dyspnoea (shortness of breath), etc. This monitoring period will last up to at least 4 hours after the first BI-1206 infusion and at least 30 minutes after every subsequent BI-1206 infusion. For rituximab infusions, this monitoring period will last up to at least 30 minutes after the end of each infusion.

Should patients develop any of the symptoms described above despite pre-medication (with or without steroids), the infusion must be stopped immediately and IV hydrocortisone 100 mg or IV dexamethasone 8 mg administered. Alternative steroid treatment may be used if clinically indicated according to Investigator’s judgement. Once the reaction has stopped, infusion of BI-1206 or rituximab may restart with a 50% reduction in the rate of infusion. If IV hydrocortisone/dexamethasone is

insufficient, the reaction may be further managed with antipyretics, anti-histamines, intra-venous sodium chloride (NaCl), bronchodilators and additional glucocorticoids as required and as per local protocols.

Patients who are to receive rituximab (Arm 2 in Parts A and B): For those patients whose lymphocyte counts are >25 x 10^9/L it is recommended to administer prednisone/prednisolone 100 mg IV shortly before rituximab infusion to decrease the rate and severity of acute infusion reactions and/or CRS. A reduced infusion rate should be considered for these patients for the first infusion and a split dosing over two days during the first week, i.e. rituximab 100mg IV Day 1 (Week 1 only) followed by rituximab 375mg/m^2 minus 100mg IV Day 2 (Week 1 only). The rate of infusion and confirmation of split dosing in subsequent weeks must be agreed with the Sponsor and CI prior to commencement of treatment.

Patients who are to receive BI-1206 (All patients): If IRRs are seen following Week 1 infusion, the Investigator may consider spilt dosing over 2 days for subsequent infusions (from Week 2 onwards) to decrease severity of reactions in subsequent doses.The rate of infusion and confirmation of split dosing must be agreed with the Sponsor and CI prior to commencement of treatment.

Patients with severe, life threatening reactions to BI-1206 or rituximab must not receive further infusions and should be withdrawn from the trial.

Investigators have the option to split the dose of BI-1206 at any point from (and including) Week 1 onwards based on clinical presentation of the patient at study entry and the Investigator's clinical judgement of what is likely to be most appropriate for an individual patient and collective study experience with giving BI-1206 to date. Once the decision to split a dose is taken, the patient must continue to receive split dosing for the duration of their study participation.

For rituximab, as per normal clinical practice, Investigators have the option to revert back to single dosing after splitting the dose.

5.9.3 Management of ocular toxicities

As described in Section 2.2.8, preclinical studies noted evidence of FcγRIIB expression on the eye. Eye examinations have therefore been included in the schedule of events to allow for assessment throughout study treatment.

If any grade of toxicity affecting the macula and/or affecting patient's vision is observed then study treatment must be stopped and intensified monitoring implemented as per the site ophthalmologist's recommendation. Restarting treatment will be considered on discussion with the PI, CI, ophthalmologist and Sponsor.

If NCI-CTCAE v4.02 Grade 1 ocular toxicity is observed which does not affect the macula or patient's vision, study treatment may continue with intensive monitoring as per site ophthalmologist's recommendation.

If Grade 2 or above ocular toxicity is observed, not affecting the macula or patient's vision, treatment must be stopped and intensified monitoring should be implemented as per site ophthalmologist's recommendation. Restarting treatment will be considered on discussion with the PI/CI, ophthalmologist and Sponsor

5.9.4 Management of thrombocytopenia (Grade 4)

If Grade 4 thrombocytopenia is noted post infusion:

- Perform daily (or as frequent as possible) full blood count (FBC) monitoring until resolution to Grade 3 or less.

- If this is not possible, then the patient should be monitored closely until resolution to Grade 3 or less AND as a minimum a FBC must be performed on the 5th day from when Grade 4 thrombocytopenia was first noted (unless there is documented resolution to Grade 3 before that point).
- Toxicity must be resolved to at least Grade 2 or lower before the next dose can commence; therefore a delay in treatment may be required.

5.9.5 Dose reductions

Patients who experience a DLT (as defined in Section 3.3) that resolves to Grade ≤1 or recovers to baseline within 7 days of the start of the DLT may recommence treatment (with BI-1206 ± rituximab), with the agreement of the PI, CI and Sponsor. The dose should be reduced to the previous dose level and rate of infusion may be reduced and agreed with the Sponsor and Investigator prior to treatment.

If the AE has not resolved to Grade ≤1 or recovered to baseline within 7 days, the patient will be taken off-study and treatment shoud be discontinued. If the patient experiences another DLT, either the same or different toxicity, further treatment is not permitted.

5.9.6 Dose delays and Treatment Discontinuation

In this trial, if a patient experiences one or more of the following toxicities related (highly probably, probably or possibly) to BI-1206 or rituximab treatment, the treatment for that patient should be delayed/modified as described. Please refer to Section 5.9.2 for actions to be taken in event of a reaction during the infusion.

Grade 1 or 2 toxicity (haematological or non-haematological) other than ocular toxicity or infusion related reaction.

No dose modifications or delays are necessary; refer to Section 5.9.3 for guidance on management of ocular toxicity, Section 5.9.2 for guidance on management of infusion related reactions.

Grade 3 or 4 Haematological toxicity that does not meet DLT definition as described in Section 3.3

Treatment with BI-1206 and rituximab, if applicable should be delayed until recovery of the patient's full blood count to Grade ≤ 2. Treatment may be delayed for a maximum of three weeks. Patients experiencing ≥Grade 3 haematological toxicity lasting longer than three weeks must not receive further treatment with BI-1206 or rituximab. Growth factor support is permissible during this period.

Grade 3 or 4 Non-haematological toxicity that does not meet DLT definition as described in Section 3.3

Refer to Section 5.9.3 for guidance on management of ocular toxicity, Section 5.9.2 for guidance on management of infusion related reactions. For other events, treatment with BI-1206 and rituximab, if applicable, should be delayed until recovery of the AE(s) to Grade ≤ 2. Treatment may be delayed for a maximum of three weeks. Patients experiencing ≥Grade 3 toxicity lasting longer than three weeks must not receive further treatment with BI-1206 or rituximab.

Please see Sections 6.2.5.6 and 6.2.11.2 for further information relating to patient withdrawal from treatment.

Modifications for logistical reasons i.e. Bank Holidays

For logistical reasons (i.e. bank holidays), treatment may be delayed by a maximum of one week or treatment may be given one day earlier (decrease time between dosing to six days during induction therapy) following agreement by CI and Sponsor, prior to commencing treatment.

5.9.7 Duration of treatment

In the induction phase, treatment should continue for four weeks 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 for any other reason. Other reasons are listed in Section 11.

The duration of treatment may be extended if dose interruptions/ delays result in an extended induction period.

5.9.8 Maintenance therapy

Patients who are deriving clinical benefit (as defined in Section 10.2) may continue at the end of the induction therapy onto maintenance therapy for up to 1 year following their first dose of BI-1206 treatment on the study. Maintenance therapy will cease if (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 for any other reason. Other reasons are listed in Section 11. As BI-1206 is at an early stage of development, the long term side-effects are unknown. Treatment will therefore not continue beyond the one year maintenance period of this study.

5.9.9 Replacement of patients

Patients who come off study due to dose limiting toxicity prior to completing four weeks of induction therapy will not be replaced. Patients who come off study prior to completing four weeks of induction therapy for any other reason will be replaced for purposes of DLT evaluation during the single and combination dose escalation cohorts. Once a RP2D dose has been established (BI-1206 monotherapy and BI-1206 + rituximab combination) patients who withdraw due to disease progression and/or unacceptable toxicity will not be replaced. Other withdrawn patients may be replaced, if considered appropriate, after discussion between the PI, CI and Sponsor.

There may be circumstances based on the emerging data from the trial or IMP availability which result in a patient not being replaced. This will be documented by the Sponsor.

5.10 Concomitant medication and treatment

Concomitant medication may be given as medically indicated. Details of the concomitant medication given must be recorded in the patient's medical records and the electronic case report form (eCRF).

Radiotherapy may be given concomitantly for the symptomatic control of lymphadenopathy; however these irradiated lesions will not be evaluable for response.

Refer to Section 5.9.2 for details of pre-medications to be administered prior to BI-1206 and/or rituximab infusions. Live vaccinations are not permitted whilst on the trial; other immunisations are permitted. Doses of prednisolone >10 mg daily (or equipotent doses of other corticosteroids) are not permitted whilst on the trial, other than as pre-medication where the patient is at risk of tumour lysis due to high tumour burden, where it has been approved by the CI and Sponsor as an alternative pre-medication or if alternative steroids are required, if clinically indicated to treat infusion related reactions as per Section 5.9.2. During the screening period, doses of up to 20mg per day may be given but the dose must be reduced to 10mg/day by Week 1 Day 1 (other than as pre-medication).

The patient must not receive any other anti-cancer therapy or investigational drugs while on the trial. Participation in an observational study is allowed.

6 PHARMACEUTICAL INFORMATION

6.1 Supply of BI-1206 and rituximab

6.1.1 Supply of BI-1206

A complete certificate of analysis and a Qualified Person (QP) certification must be provided with each batch of the investigational medicinal product (IMP): BI-1206 and be retained in the Pharmacy File.

For information on BI-1206 and re-ordering of supplies, contact the Clinical Research Associate (CRA)/Clinical Study Manager (CSM) responsible for the trial who will arrange further supplies.

BI-1206 will be manufactured by:

Nova Laboratories Limited

[redacted]

BI-1206 will be stored, labelled and distributed by:

Cancer Research UK Formulation Unit

[redacted]

The distributor (Cancer Research UK Formulation Unit) must provide confirmation of the shipment to the CSM/CRA on despatch of the IMP.

The primary and secondary packaging for the IMP will be labelled according to Eudralex Volume 4: Annex 13 'Investigational Medicinal Products' of the European Union guide to Good Manufacturing Practice (GMP).

Prior to despatch of BI-1206 to the clinical trial site a label detailing the Investigator's name and site name and address will be added by the Manufacturing Authorisation Holder in accordance with GMP to the secondary packaging (box).

An example of the approved label(s) can be found in the TMF and site Pharmacy File.

6.1.2 Supply of rituximab

Rituximab will be considered an IMP as patients will not be taking the drug before enrolment on this trial. Rituximab is licensed for clinical use in the UK and EU and is marketed under several different brand names and will be used in accordance with the respective SmPC. The investigators will be responsible for their own supply of rituximab. Prior to dispensing rituximab will be labelled by the Pharmacy according to Eudralex Volume 4: Annex 13 'Investigational Medicinal Products' of the EU Guide to Good Manufacturing Practice. The label applied by Pharmacy will be approved by CR-UK and an example of the approved label for rituximab will be filed in the Pharmacy Folder. Sufficient quantities of rituximab will be dispensed to cover the prescribed dose (as per Section 6.2).

Rituximab will be dispensed from the hospital pharmacy on a per patient basis.

As per Section 2.2.7, it should be noted rituximab biosimilars may be used in this clinical trial (**Sponsor must be notified prior use)**. For additional information concerning rituximab, please refer to the SmPC specific to the brand used. Note the rituximab SmPC included in the IB Package supplied to the support the current clinical trial will be used as the RSI for rituximab in this trial.

6.2 Pharmaceutical data

6.2.1 Formulation of BI-1206

BI-1206 will be supplied as a concentrate for solution for infusion (5mL fill volume) in 5 mL Type 1 clear glass vials with a concentration of 10 mg/mL. [redacted]

6.2.2 BI-1206 storage conditions

All supplies must be stored in a secure, limited access storage area.

BI-1206 must be stored in its original packaging at 2-8°C, protected from light.

6.2.3 Method of preparation of BI-1206 for administration

Good aseptic practice must be employed when preparing solutions of BI-1206 for infusion.

[redacted]

Please refer to the Pharmacy and Drug Administration guidelines located in the Pharmacy File for additional guidance.

Each vial of BI-1206 is for single use only. Any unused contents and/or vials dispensed for patient use must be destroyed as per local policies and accounted for as described in Section 6.3.1.

6.2.4 Stability and labelling of the diluted BI-1206

After removal from the refrigerator and dilution [redacted], BI-1206 solution can be kept at ambient temperature. From a microbiological point of view, the administration should be performed as close as possible to the preparation of the diluted drug. For the 0.4mg dose level the diluted drug must be administered within 24 hours of dilution. For all other dose levels (2mg upwards) the diluted drug must be used within 48 hours of dilution. Refer to the handling instructions in the Pharmacy File for further details. Labelling requirements for the reconstituted BI-1206 for infusion can be found in the Pharmacy File.

6.2.5 BI-1206 administration

Before administration, the exact dosage must always be double-checked by a second suitably qualified person. All checks and double-checks must be documented (signed and dated) and the documentation must be available for the CRA/CSM to verify.

6.2.5.1 BI-1206 administration for 0.4 mg dose level

BI-1206 will be administered as a slow IV infusion using a syringe driver over a fixed interval of 30 minutes.

6.2.5.2 BI-1206 administration for doses from 2 mg to 10 mg

BI-1206 will be administered as a slow IV infusion using an infusion pump over a fixed interval of 30 minutes.

6.2.5.3 BI-1206 administration for the 50mg dose level

BI-1206 will be administered as a slow IV infusion using an infusion pump at an initial rate of 50 mg/hr. If no adverse effects are seen the rate of infusion may be increased at 30 minute intervals, as specified in the Pharmacy and Drug Administration Guidelines.

6.2.5.4 BI-1206 administration at doses above 50mg

First infusion (Week 1)

BI-1206 will be administered as a slow intravenous infusion at an initial rate of 50 mg/hr. If no adverse effects are seen the rate of infusion may be increased at 30 minute intervals, up to a maximum rate of 400 mg/hr, as specified in the Pharmacy and Drug Administration Guidelines.

Subsequent infusions (Week 2 onwards)

BI-1206 will be administered as a slow intravenous infusion at an initial rate of 100 mg/hr. If no adverse effects are seen the rate of infusion may be increased at 30 minute intervals, up to a maximum rate of 400 mg/hr, as specified in the Pharmacy and Drug Administration guidelines.

The Sponsor and Investigators will review and revise the infusion rates and may adjust these for subsequent cohorts in Part A and Part B.

In any event, the maximum rate of infusion for BI-1206 administration on this trial is 400 mg/hr.

6.2.5.5 Pre-medications prior to antibody administration

Refer to Section 5.9.2 for details of pre-medications to be administered prior to BI-1206 infusions. Pre-medications will be supplied by the hospital pharmacy.

6.2.5.6 Monitoring during infusion

Refer to Section 5.9.2 or details of monitoring requirements during the infusion.

If no reactions are observed, the total infusion time should be no more than 10% shorter than the expected time when given according to the infusion rates detailed above.

If a BI-1206 infusion is interrupted due to an adverse event (AE) and a full dose is not given, the Sponsor and CI should be informed. The case should be discussed and agreement from the Sponsor and CI obtained regarding continuation of treatment in subsequent weeks.

Please see Section 5.9.6 'Dose delays/treatment discontinuation' which also offers guidance for re-challenging patients post related AE observation.

Patients with severe, life threatening reactions to BI-1206 must not receive further infusions and should be withdrawn from the trial.

Following an IRR event, if the patient is unable to receive the next full dose of BI-1206 due to a subsequent IRR event, the Investigator should consider withdrawing the patient from further BI-1206 treatment – this should be discussed with the Sponsor and CI.

6.2.6 BI-1206 Vein extravasation/accidental spillages

BI-1206 is not a vesicant. Vein extravasation and accidental spillages should be dealt with according to hospital policy.

6.2.7 Formulation of rituximab

The following text is an excerpt from the SmPC for rituximab (MabThera®). For further information please refer to the full text in the rituximab SmPC specific to the brand being used.

Rituximab will be supplied as vials of 10 mL or 50mL with a 10 mg/mL concentration, for intravenous use after dilution. Rituximab is provided in sterile, preservative-free, non-pyrogenic, single use vials.

6.2.8 Storage conditions of rituximab

All supplies must be stored in a secure, limited access storage area.

Rituximab must be stored in its original packaging in a refrigerator (2-8ºC). Keep the container in the outer carton, in order to protect from light.

Each vial of rituximab is for single use only. Any unused contents and/or vials dispensed for patient use must be destroyed as per local policies and accounted for as described in Section 6.3.2.

6.2.9 Method of preparation of rituximab for administration

Good aseptic practice must be employed when preparing solutions of rituximab for infusion.

The approved diluents for dilution of rituximab are sterile, pyrogen-free NaCl 9 mg/mL (0.9%) solution for injection or 5% D-glucose in water.

Please refer to the SmPC specific to the brand of rituximab being used for detailed instructions on how to reconstitute rituximab.

6.2.10 Stability and labelling of the diluted rituximab

The prepared infusion solution of rituximab is physically and chemically stable for 24 hours at 2 -8°C and subsequently for 12 hours at room temperature, provided dilution has taken place in controlled and validated aseptic conditions.

6.2.11 Rituximab administration

Before administration, the exact dosage must always be double-checked by a second suitably qualified person. All checks and double-checks must be documented (signed and dated) and the documentation must be available for the CRA/CSM to verify.

Rituximab will be administered at the following rates (as per the SmPC specifc to the brand being used).

<u>First infusion</u>

The initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h.

For those patients whose lymphocyte counts are >25 x 10^9/L, a reduced infusion rate should be considered for the first infusion and dosing may be split over two days during the first week, i.e. rituximab 100mg IV Day 1 (Week 1 only) followed by rituximab 375mg/m^2 minus 100mg IV Day 2 (Week 1 only). The Sponsor and CI must agree the required infusion rate and any split dosing requirements and communicate these to the investigator site before the start of treatment.

<u>Subsequent infusions</u>

Subsequent doses can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minute intervals, to a maximum of 400 mg/h.

Patients with severe, life threatening reactions to rituximab must not receive further infusions and should be withdrawn from the study.

6.2.11.1 Pre-medications prior to rituximab administration

Refer to Section 5.9.2 for details of pre-medications to be administered prior to rituximab infusions. Pre-medications will be supplied by the hospital pharmacy.

6.2.11.2 Monitoring during infusion

Refer to Section 5.9.2 for details of monitoring requirements during the infusion.

If a rituximab infusion is interrupted due to an AE and a full dose is not given, the Sponsor and CI should be informed. The case should be discussed and agreement from the Sponsor and CI obtained regarding continuation of treatment in subsequent weeks.

Patients with severe, life threatening reactions to rituximab must not receive further infusions and should be withdrawn from the trial.

Following an IRR event, if the patient is unable to receive the the next full dose of rituximab due to a subsequent IRR event, the Investigator should consider withdrawing the patient from further rituximab treatment – this should be discussed with the Sponsor and CI.

6.2.12 Vein extravasation/accidental spillages

Rituximab is not a vesicant. Vein extravasation and accidental spillages should be dealt with according to hospital policy.

6.3 Drug accountability

6.3.1 BI-1206 accountability

Accurate records of all BI-1206 shipments, vials dispensed, and all BI-1206 returned must be maintained. This inventory record must be available for inspection at any time by CRAs or CSM of Cancer Research UK's Centre for Drug Development (CDD). All IMP supplies are to be used only in accordance with this protocol and under the supervision of the Investigator.

The Investigator undertakes not to destroy any unused or returned IMP unless authorised to do so by the CDD. Any unused IMP must be destroyed according to hospital procedures and properly accounted for using the IMP Destruction Form and also on the IMP Accountability Record. During the course of the trial the CRA will check the numbers of vials of BI-1206 shipped to the centre, the number used and the number destroyed or returned. The pharmacy will give an account of any discrepancy.

6.3.2 Rituximab accountability

Accurate records of all rituximab doses dispensed, including the brand used, expiry date and batch number should be recorded. These records must be available for inspection at any time by CRAs or CSM.

During the course of the trial the CRA will check the doses of rituximab prepared and administered to patients on this trial. The pharmacy will give an account of any discrepancy.

7 INVESTIGATIONS SCHEDULE

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 reported results. These results must be available for source data verification (SDV). Laboratory reference ranges, including effective dates, and evidence of laboratory accreditation must be obtained from all laboratories used.

The Investigator or delegate must inform Cancer Research UK's CDD of any changes to the laboratory normal ranges or to any laboratory accreditation and provide any new documentation.

7.1 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.

Please also refer to the tabulated Schedule of Assessments in Section 7.6.

7.1.1 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 BI-1206 dosing then the Investigator should consider whether repeat consent should be obtained from a patient.

Only the PI and those Sub-Investigator(s) with delegated responsibility by the PI, and who have signed the Delegation Log, are permitted to obtain 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 date of the signatures of both the patient and the PI/Sub- Investigator obtaining informed consent should be the same.

The PI or the Sub-Investigator must inform the patient about the background to the study, and present knowledge of the normal management of their disease and BI-1206 and rituximab (if applicable). They must also ensure that the patient is aware of the following points:

- That treatment with BI-1206 (or, if applicable BI-1206 in combination with rituximab) is new and that the exact degree of activity is at present unknown, but that treating him/her will contribute to further knowledge.
- The known toxicity of BI-1206 and rituximab, if applicable and the possibility of experiencing side-effects.
- 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 9.10).
- 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 Informed Consent Document (ICD) must be given to the patient to keep and the original ICD, must be filed in the Investigator Trial File (ITF) (unless otherwise agreed that the original document will be filed in the medical records and a copy kept in the ITF).

7.1.1.1 CD32b and CD20 expression testing

Part A (CD32b testing):

- As part of the main screening and consent process, the patient will be asked to provide an initial blood sample or historical (or routine care) biopsy sample for CD32b analysis.
- The blood sample wil be taken and the archival tumour requested, post consent to the main study. There is no limit on the date of the archival tumour being tested.
- Testing may also be performed on any available bone marrow or lymph node sample which is taken during the screening process.

  The results of this analysis is for information only.

Part B (CD32b and CD20 testing):

- Pre screening consent, as per Section 7.1.2, must be given by the patient before analysis can take place.
- For CD32b testing, the available tissue or blood must be taken and tested with 6 months of main study consent.
  For CD20 testing, for patients that are refractory to rituximab, i.e either progressing whilst on rituximab based therapy (induction or maintenance) or progressing within 6 months of their last dose of rituximab, a biopsy should be performed prior to study entry to ensure that there is continued expression of CD20.

  The results of this analysis will inform the patient's eligibility for the main trial.

To note: For CD32b testing, patients with follicular lymphoma and any other patient group where B cells are not present in the circulation, blood samples should not be provided, only tissue e.g. lymph node, bone marrow or any other secondary tumour sample.

7.1.2 Pre-Screening – Part B only

Patients must give separate written informed consent before analysis of a historical biopsy sample (or a new blood sample, taken for CD32b (CD20 if required) positivity by immunohistochemistry or flow cytometry, if not previously performed. This Pre-Screening test may be performed at any point prior to the patient providing written informed consent for the full trial. For CD32b testing in Part B, the available tissue or blood must be taken and tested with 6 months of main study consent.

CD20 expression is required for all patients receiving BI1206 and rituximab in combination.

7.1.3 Baseline Evaluations

The following must be performed/obtained **before** the patient receives their first dose of BI-1206 or rituximab. Existing results such as radiological measurements may be used even where these investigations were performed prior to the patient's provision of information consent for the study if they were performed within the required time window.

- Written informed consent (as detailed in Section 7.1.1) before any protocol-specific procedures are carried out. Note for eligible patients, 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 9 for further details).

  For Part B patients: following pre-screening consent, safety reporting is applicable as per Section 9.6.

- Bone marrow aspirate and/or lymph node biopsy. This can be performed for disease assessment purposes at the patient's local hospital as part of their routine care. If performed solely for purposes of the trial, the patient must first consent to the main study. This must be performed/obtained **within eight weeks before** the patient receives their first dose. Aspirate

will be taken for flow cytometry analysis as detailed in Section 8.3.2 and CD32b/CD20 confirmation of disease as described in Sections 8.2.1 and 8.2.2.

- Demographic details (**within four weeks before** the patient receives their first dose of BI-1206 or rituximab on study.)
- Medical history including prior diagnosis, prior treatment, concomitant conditions/diseases and baseline symptoms, concomitant treatment (**within four weeks before** the patient receives their first dose of BI-1206 or rituximab on study).
- **For patients recruited in Part A:** CD32b expression assessed centrally by blood, bone marrow sample and/or lymph node sample sent during screening assessments.
- **For patients recruited in Part B:** Confirmation of CD32b+ disease. Confirmed centrally by blood, bone marrow or lymph node biopsy sample taken within 6 months of study entry as described in Section 8.2.1. **Note: testing of any archival sample for the sole purpose of determining trial eligibility should only take place once the patient has provided informed consent for this analysis either by signing the screening consent form or the main consent form for the study.** If CD32b status has already been assessed at the trial approved laboratory according to the trial agreed method in the 6 months prior to main study consent, these results can be used for inclusion and there is no requirement for retest. If surgery is required to obtain a new lymph node biopsy sample, then tissue should be retained for analysis of tissue markers as described in Section 8.4.4.
- **For patients receiving rituximab:** Confirmation of CD20+ disease; confirmed by blood, bone marrow or lymph node biopsy sample. In patients that are refractory to rituximab, i.e either progressing whilst on rituximab based therapy (induction or maintenance) or progressing within 6 months of their last dose of rituximab, a biopsy should be performed prior to study entry to ensure that there is continued expression of CD20.. Please note: if no B cells are present in circulation, do not send a blood sample for CD20 disease assessment.
- Serum Immunoglobulins – IgA, IgM & IgG (**within four weeks before** the patient receives their first dose of BI-1206 or rituximab on study).
- Beta-2-microglobulin (**within four weeks before** the patient receives their first dose of BI-1206 or rituximab on study).
- Radiological Disease Assessments (**within four weeks before** the patient receives their first dose of BI-1206 or rituximab on study).
    - **Patients with CLL:** Computerised tomography (CT) scan of neck, chest, abdomen and pelvis must be performed **within four weeks before** the patient receives their first dose of BI-1206 or rituximab on study.
    - **Patients with Lymphoma (other than Waldenström's macroglobulinemia):** CT scan of neck, chest, abdomen and pelvis and a fluorodeoxyglucose positron emission tomography ([^{18}F]FDG-PET) scan must be performed for those Patients with PET-avid disease **within four weeks before** the patient receives their first dose of BI-1206 or rituximab on study.
    - **Patients with Waldenström's macroglobulinemia:** CT scan of neck, chest, abdomen and pelvis must be performed **within four weeks before** the patient receives the first dose of BI-1206 or rituximab on study. If there is a concern regarding high grade transformation then a [^{18}F]FDG-PET scan should also be performed **within four weeks before** the patient receives their first dose of BI-1206 or rituximab on study.
    - **Patients with Waldenström's macroglobulinemia:** (**within four weeks before** the patient receives their first dose of BI-1206 or rituximab on study)**:** a blood sample should be taken for assessment of serum paraprotein electrophoresis and immunofixation. Please note, this serum paraprotein is also sometimes referred to as serum monoclonal protein IgM, but should not be confused with IgM assessed as part of the immunoglobulin sample described above as this is a different assessment or rituximab on study.

- Assessment of Hepatitis B and C and HIV positivity (**within four weeks before** the patient receives their first dose of BI-1206 or rituximab on study).
- Electrocardiogram (ECG) (**within four weeks before** the patient receives their first dose of BI-1206 or rituximab on study)*;*
- Female patients able to have children must have a negative result on a human chorionic gonadotropin (HCG) pregnancy test (serum or urine test is acceptable) **within two weeks before** the patient receives their first dose of BI-1206 or rituximab on study.
- Clinical disease measurements, if applicable (i.e. patients with clinically assessable disease). **This must be performed within one week before the patient receives their first dose** of BI-1206 or rituximab on study.
- Complete physical examination (**within one week before** the patient receives their first dose of BI-1206 or rituximab on study);
- Height, weight, body surface area (BSA) (**within one week before** the patient receives their first dose of BI-1206 or rituximab on study**.**)
- WHO performance status, temperature, seated blood pressure (BP), pulse rate and oxygen saturation levels (Sa02) (**within one week before** the patient receives their first dose of BI-1206 or rituximab on study);
- Laboratory tests (blood/urine samples) to confirm eligibility (to be repeated, if not performed **within one week before** the patient receives their first dose of BI-1206 or rituximab on study).
    - Haematology – haemoglobin (Hb), platelets, white blood cells (WBC) with differential count (eosinophils, basophils, neutrophils and lymphocytes), CD3 T Lymphocytes, CD19 B lymphocytes (usually as part of TBNK or lymphocyte subset panel).
    - Biochemistry – lactate dehydrogenase (LDH), sodium, potassium, calcium (adjusted), phosphate, urea, creatinine, total protein, albumin, bilirubin, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)
    - Urinalysis – protein and blood
    - Coagulation–partial thromboplastin time (PTT/APTT) and either prothrombin time (PT) or international normalised ratio (INR).
- Eye examination performed by appropriately trained member of site staff including: slit lamp assessment, retinal examination and measurement of visual acuity (**within four weeks before** the patient receives their first dose of BI-1206 or rituximab on study).

7.2 Evaluations during Induction Therapy (Weeks 1-8)

- Symptom-directed physical examination: if clinically indicated, a symptom-directed physical examination is to be performed within 24 hours prior to each BI-1206 administration and at Week 5. Patients in **Cohort 1, Arm 1 only** will also attend for this assessment at 72 hours post infusion at Weeks 1 to 4 (on Days 4, 11, 18 and 25).
- WHO performance status, to be recorded within 24 hours prior to each dose of BI-1206 or rituximab and at Week 5. This will also be assessed for patients in Cohort 1, Arm 1 only, 72 hours post infusion at Weeks 1 to 4 (on Days 4, 11, 18 and 25) for dose escalation purposes.Temperature, pulse rate, seated BP, to be recorded within 2 hours prior to each dose of BI-1206 or rituximab and at Week 5. These will also be assessed for patients in Cohort 1 at Day 4 of Weeks 1 to 4 (Days 4, 11, 18 and 25) for dose escalation purposes.
- During the first BI-1206 infusion for each patient: Pulse rate, temperature and seated BP must be measured every 15 minutes for the first hour and then within every 30 minutes until the end of the infusion. Where the infusion lasts less than an hour these should be measured every 15 minutes.
- During second and subsequent BI-1206 infusions and all rituximab infusions for each patient: Pulse rate, temperature and seated BP must be measured within every 30 minutes until the end of the infusion.

- After the BI-1206 or rituximab infusions for each patient: Pulse rate, temperature and seated BP must be measured at 30 minutes (± 5 minutes) after the end of the infusion and, in Part A, Week 1 at 2 and 4 hours after the end of the BI-1206 infusion.

  In Arm 2, where BI-1206 and rituximab are given on the same day, the pulse, temperature and seated BP should be measured within 2 hours prior to the BI-1206 infusion, at the end of the BI-1206 infusion, within every 30 minutes between the infusions prior to the start of the rituximab infusion and at the end of the rituximab infusion.

- **For patients receiving rituximab treatment*:*** Weight measured during screening should be used for BSA calculation for induction therapy.

- Adverse events and concomitant treatments: At each visit, before each BI-1206 or rituximab administration, 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 BI-1206 and/or rituximab must be recorded in the medical records.

  All AEs must be graded according to NCI CTCAE Version 4.02. (See Section 9 for further details regarding AE reporting requirements).

  Any concomitant treatment must be recorded in the medical records (See Section 9 for further details regarding AE reporting requirements).

- Laboratory tests:

  Haematology, biochemistry and urinalysis: must be repeated before each BI-1206 administration (and before each rituximab administration if given on a different day to BI-1206), Week 1, Day 4 and at Weeks 5 and 8. Laboratory tests can be performed up to 24 h prior to each infusion but results must be available and reviewed by the investigator before BI-1206 or rituximab is given. These will also be repeated for patients treated in Cohort 1, Arm 1 only at Day 4 of Weeks 1 to 4 for dose escalation purposes (Days 4, 11, 18 and 25).

  - Haematology: detailed in Section 7.1.3.
  - Biochemistry: detailed in Section 7.1.3.
  - Urinalysis: detailed in Section 7.1.3.

- If split dosing is implemented, laboratory tests will be relative to the first infusion administered each week then as clinically indicated on the second day.

- Beta-2-microglobulin levels will be assessed at Week 8.

- ECG: performed if clinically indicated.

- Eye exam: performed as described in Section 7.1.3 at Week 8 and otherwise if clinically indicated.

- Serum Immunoglobulins – IgA, IgM & IgG levels will be assessed at Week 8.

- **Patients with Waldenström's macroglobulinemia:** a blood sample should be taken for assessment of serum paraprotein at Week 8 (electrophoresis and immunofixation)

- Radiological disease assessments:

- **CLL Patients:** CT scan of neck, chest, abdomen and pelvis will be performed at Week 8.

- **Patients with lymphomas:** CT scan of neck, chest, abdomen and pelvis and for non Waldenströms Macroglobulinaemia patients, an [^{18}F] FDG-PET scan if positive at baseline will be performed at Week 8.

- Bone marrow aspirate and lymph node biopsy:

  - **CLL Patients:** Those patients who had positive test at baseline and who show a complete response on Week 8 assessments will have a sample taken for disease assessment. If a sample is being taken for disease assessment, then aspirate will also be taken for flow cytometry analysis as detailed in Section 8.3.2.

- **Patients with lymphomas:** Those patients who had positive test at baseline and who show a complete response on Week 8 assessments will have a sample taken for disease assessment. If a sample is being taken for disease assessment, then aspirate will also be taken for flow cytometry analysis as detailed in Section 8.3.2.
- [redacted]

- Blood samples for PK analysis, will be taken at each of the time points specified in Section 8.3.
- Pharmacodynamic blood samples for assessment of CD32b B-lymphocyte levels, [redacted] and anti-drug antibody levels, should be taken pre- and post treatment as described in Sections 8.3 and 8.4.
- Oxygen Saturation levels (Sa02) to be performed pre-dose during Week 1 – 4 (induction therapy only) and otherwise as clinically indicated.

7.3 Evaluations during maintenance therapy

For patients who demonstrate clinical benefit (as defined in Section 10.2) at Week 8 following their induction therapy, further treatment with BI-1206 (± rituximab) may continue. The patient will receive the same dose of BI-1206 ± rituximab as they received during their induction therapy. Starting from Week 8 onwards (post scan results) maintenance therapy will continue every eight weeks (± 2 weeks) from the first maintenance dose for up to one year after the first dose of BI-1206 on the study.

- Symptom-directed physical examination: If clinically indicated, a symptom-directed physical examination will be performed prior to BI-1206 administration.
- WHO performance status to be recorded prior to BI-1206 or rituximab.
- **For patients receiving rituximab:** For maintenance treatment, weight should be measured prior to each dose and BSA recalculated if the patient's weight has changed by more than 10% from the weight used for the current BSA (i.e. weight at 1st maintenance will be compared to from weight measured at screening).
- Pulse rate, temperature and seated BP must be measured within 2 hours prior to each infusion, within every 30 minutes during the infusion and at 30 minutes (± 5 minutes) after the end of the infusion

  Where BI-1206 and rituximab are given on the same day, the pulse, temperature and seated BP should be measured within 2 hours prior to the BI-1206 infusion at the end of the BI-1206 infusion, within every 30 minutes between the infusions, prior to the start of the rituximab infusion and at the end of the rituximab infusion.
- Adverse events and concomitant treatments: At each visit, before each BI-1206 administration, 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 BI-1206 and/or rituximab 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 electronic case report form (eCRF).
- Haematology, biochemistry and urinalysis: must be repeated before each BI-1206 administration (and before each rituximab administration if given on a different day to BI-1206).
  - Haematology: See Section 7.1.3.
  - Biochemistry: See Section 7.1.3.
  - Urinalysis: See Section 7.1.3.
- ECG: performed if clinically indicated.
- Eye exam: performed if clinically indicated.

- Assessment of disease:

  A CT scan will be performed every 16 weeks (± 2 weeks but must be performed and reported before the patient's BI-1206 infusion) and at off-study where a scan has not been performed in the previous 8 weeks.

  Should the Investigator assess that the patient is no longer deriving clinical benefit (as defined in Section 10.2) from continued maintenance therapy, the patient will be withdrawn from the trial.

  Patients with lymphomas: For patients who have [^{18}F]FDG PET-avid disease at baseline whose CT scans show a complete response, an [^{18}F]FDG-PET scan should be performed within 4 weeks of receipt of the CT scan results.

  Patients with Waldenström's macroglobulinemia: a blood sample should be taken for assessment of serum paraprotein. Normal serum IgM levels should also be measured.

- Bone marrow aspirate:
  - **CLL Patients:** Those patients who had positive test at baseline and who show a complete response for the first time at a disease assessment during the maintenance period will have a bone marrow sample taken. [redacted]
  - **Patients with lymphomas:** Only those patients who had positive test at baseline and who show a complete response for the first time at a disease assessment during the maintenance period will have a bone marrow sample taken. [redacted]
- Pharmacodynamic blood sample for assessment of anti-drug antibody levels, should be taken as described in Section 8.3.
- Blood samples for PK analysis, will be taken at each of the time points specified in Section 8.3.

7.4 Evaluations at 'off-study' visit

The off-study visit will occur when a patient will no longer continue on the treatment portion of the trial (either induction or maintenance treatment). This may be because of any of the reasons outlined in Section 11 or for patients who have completed a year of maintenance therapy. If a patient comes off-study following the Week 8 assessments and prior to commencing maintenance therapy the Week 8 assessments will be considered the "off-study" assessments. At this visit the following investigations where possible will be performed:

- A symptom-directed physical examination including WHO performance status, temperature, pulse rate and seated BP.
- Haematology (see Section 7.1.3).
- Biochemistry (see Section 7.1.3).
- Urinalysis (see Section 7.1.3).
- Serum Immunoglobulins – IgA, IgM & IgG levels will be assessed.
- Beta-2-microglobulin.
- Eye examination as described in Section 7.1.3 within ± 2 weeks of the off-study visit date.
- ECG: performed if clinically indicated.

- Assessment of disease (unless disease progression has been noted at an earlier assessment or, if the patient has gone on to maintenance therapy and an assessment has been performed within the previous eight weeks (56 days)):

  CT scan to assess tumour burden within ± 2 weeks of the off-study visit date;

  - **Patients with lymphomas:** For patients who have FDG PET-avid disease at baseline whose CT scans show a complete response, an FDG-PET scan should be performed within ± 2 weeks of the off-study visit date.

  - **Patients with Waldenström's macroglobulinemia:** a blood sample should be taken for assessment of serum paraprotein.

- Bone marrow aspirate:
  - **CLL Patients:** Those patients who had positive test at baseline and who show a complete response for the first time at a disease assessment at the off-study visit will have a bone marrow sample taken. [redacted]
  - **Patients with lymphomas:** Only those patients who had positive test at baseline and who show a complete response for the first time at a disease assessment at the off-study visit will have a bone marrow sample taken. [redacted]
- Pharmacodynamic blood sample for assessment of ADA levels, should be taken as described in Section 8.3.
- Assessment of AEs.
- Review of concomitant treatments.

7.5 Follow-up

7.5.1 Safety follow-up

For eligible patients, SAE and AE monitoring will continue until 125 days after the last administration of BI-1206 and or rituximab on study (whichever is later) or until the patient starts another anti-cancer therapy (see Section 9.6). Any drug-related AEs still ongoing after this period will be followed up monthly until resolution to baseline or stabilisation, unless the patient starts another anti-cancer therapy.

Should an Investigator become aware of any drug-related SAEs after this period (even if the patient has started another anti-cancer therapy) these must also be reported to the CDD within the expedited timelines in Section 9.7.

7.5.2 Efficacy and survival follow-up

All patients will be followed up for survival at one year (to be calculated from the date of their first BI-1206 treatment) and subsequently until the last patient has completed one year of follow-up from the date of their first BI-1206 treatment.

Contact will be made at routine follow-up appointments (approximately every 16 weeks) to assess survival status. Information on disease status will also be captured for any patients who have not shown progressive disease at the time of their off-study visit.

Survival (and if applicable, disease status) will be captured every approximately every 16 weeks from the off study visit, up to 1 year after the patient started study treatment and then every 6 months until the last patient has completed one year of follow-up from the date of their first BI-1206 treatment.

7.6 Schedule of events

Observation/Investigation	Screening		Induction Therapy								Week 5	Week 8	Maintenance Therapy (i)	Off-study visit	Survival Follow-up
			Week 1		Week 2		Week 3		Week 4						
	Within 4 weeks	Within 1 week	Day 1	Day 4	Day 8	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29 (+3 days)	Day 50 (+1 week) Decision point: Patient to continue onto maintenance therapy or off study	Every 8 weeks (±2 wks)		Every 16 weeks up to one year, then every 6 months or at clinic visits.
Written informed consent	X														
Demographics & Medical history	X														
Adverse event evaluation	From date of informed consent		Continually review								X	X	X	X (k)	
Concomitant treatments	X	X	Continually review								X	X	X	X	
Confirmation of CD20+ disease (patients treated with rituximab) (a)	X														
CD32b expression in Part A/ CD32b+ disease in Part B	X (q)														
Disease assessment by CT	X											X	X (j)	X (j)	
Clinical disease assessment (if applicable)		X										X	X (j)	X (j)	
FDG-PET (Non-WM lymphoma patients)	X											X	(X (j))		
Serum Paraprotein (WM patients)	X											X	X	X	
Bone marrow aspirate (and trephine) (m)	X											X (if CR)	X (if CR (j))	X (if CR)	
Pregnancy test (b)		X													
Height, weight, BSA (c)		X											X (c)		
Physical examination (d)		X	X								X	X	X	X	
Hep B/ C/ HIV	X														
Temperature, blood pressure, pulse and SaO2 (p)		X	X		X		X		X		X	X	X	X	
WHO performance status		X	X	(X)[l]	X	(X)[l]	X	(X)[l]	X	(X)[l]	X	X	X	X	

Observation/Investigation	Screening		Induction Therapy								Week 5	Week 8	Maintenance Therapy (i)	Off-study visit	Survival Follow-up
			Week 1		Week 2		Week 3		Week 4						
	Within 4 weeks	Within 1 week	Day 1	Day 4	Day 8	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29 (+3 days)	Day 50 (+1 week) Decision point: Patient to continue onto maintenance therapy or off study	Every 8 weeks (±2 wks)		Every 16 weeks up to one year, then every 6 months or at clinic visits.
Haematology and biochemistry (e) **including B and T Lymphocytes**		X	X	X	X	(X)[l]	X	(X)[l]	X	(X)[l]	X	X	X	X	
Urine sample for urinalysis		X	X	X	X	(X)[l]	X	(X)[l]	X	(X)[l]	X	X	X	X	
Serum Immunoglobulins (IgA, IgG, IgM)	X											X	(X, WM pts IgM every 16 wks)	X	
Beta-2-microglobulin	X											X		X	
Coagulation		X													
Autoimmune assessment		X									X	X	X	X	
Eye examination (f)	X		(X)								(X)	X	(X)	X	
Electrocardiogram (ECG) (g)	X		(X)								(X)	(X)	(X)	(X)	
Premedication (h)			X		X		X		X				X (i)		
BI-1206/ rituximab administration (h)			X		X		X		X				X (i)		
PK sampling (see Section 8)			X	X	X	X	X	X	X	X			X		
PD sampling (see Section 8)		X	X	X (o)	X	X (o)	X	X (o)	X	X (o)	X	X	X	X	
Follow-up contact for survival/progression (n)															X

(a) In patients that are refractory to rituximab, i.e either progressing whilst on rituximab based therapy (induction or maintenance) or progressing within 6 months of their last dose of rituximab, a biopsy should be performed prior to study entry to ensure that there is continued expression of CD20.

(b) Pregnancy test: For female patients of child bearing potential within 2 weeks before receiving BI-1206.

(c) Weight measured during screening should be used for BSA calculation for induction therapy. For maintenance treatment, weight should be measured prior to each dose and BSA recalculated if the patient's weight has changed by more than 10% from the weight used for the current BSA (i.e. weight at 1st maintenance will be compared to weight measured at screening), there is no need to re-measure height.

(d) Complete physical examination to be performed pre-study then all subsequent examinations can be symptom-directed or as clinically indicated.

(e) Clinical laboratory assessments should be performed prior to each BI-1206 infusion (and before each rituximab administration if given on a different day to BI-1206). Laboratory tests can be performed up to 24 h prior to each infusion but results must be available and reviewed by the investigator before BI-1206/rituximab is given. In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia a full blood count must be performed at least on Day 5 (Day 10 for neutropenia) after the onset of the event to determine if a dose limiting toxicity has occurred. Monitoring must continue until resolution to Grade 3 or less. At screening, GFR measurement may be required if there is a concern regarding the calculated creatinine clearance measurement).

If split dosing is implemented, laboratory tests will be relative to the first infusion administered each week then as clinically indicated on the second day.

(f) Eye exam, performed by ophthalmologist to be performed at screening, week 8 and off-study and otherwise as clinically indicated.

(g) ECG to be performed pre-study and otherwise as clinically indicated.

(h) For patients recruited to Part A & B, Arm 2, rituximab to be given on Day 2 post BI-1206 at Week 1. If infusion time permits, then subsequent doses of rituximab will be given on the same day as BI-1206. Maintenance treatment (from Week 8) will only be given if a patient is deemed eligible to continue on to maintenance treatment following Week 8 assessments.

If split dosing is implemented, laboratory tests will be relative to the first infusion administered each week then as clinically indicated on the second day.

(i) Maintenance therapy will only be given to those patients who demonstrate stable or responding disease and will start after the Week 8 scan results following induction therapy confirming patient is eligible for maintenance treatment. Patients will receive the same dose of BI-1206 (and rituximab if received) as in their induction therapy from week 8 onwards (i.e. Week 9 or 10) and every 8 weeks (± 2 weeks) from the first maintenance dose, for up to one year from first induction dose.

(j) A CT scan to assess the patient's tumour burden to be performed at Week 8 (prior to commencing maintenance therapy) and then every 16 weeks (± 2 weeks) during maintenance therapy and at off-study. Patients with Waldenstrom's macroglobulinaemia will also have serum paraprotein samples taken at these time points. If a complete response is noted, a bone marrow biopsy may be performed and in a lymphoma patient with PET-avid disease a FDG-PET scan will also be performed. A scan is only required at Off-study if no appropriate disease assessment has been performed recently (at week 8 or as required on maintenance).

(k) Monthly follow-up required ONLY for those AEs and SAEs considered drug-related (highly probable, probable or possible) and present at off-study. Monthly follow-up for AEs to continue until resolution, return to baseline, stabilisation or patient starts another anti-cancer treatment.

(l) Day 11, 18, 25 assessments performed for patients in Cohort 1, Arm 1 only.

(m) Bone marrow aspirate samples are used for pharmacodynamic analysis, trephine samples are to be taken where required for disease assessment, if a sample is taken as part of routine care within 8 weeks prior to starting on the study a repeat baseline sample is not required. After baseline, a bone marrow sample is only required for disease assessment to confirm at complete response.

(n) Follow-up will continue until the last patient has completed one year of follow-up from the date of their first BI-1206 treatment.

(o) Samples may also be taken on Day 2 and/or Day 4 after each weekly dose during weeks 1-4, emerging data will be reviewed at dose review meetings and a decision will be made for the following cohort as to whether or not these samples are required. Schedule may also differ between arms due to logistical reasons, refer to Study Laboratory Manual for details

(p) Oxygen saturation levels (SaO2) to be performed pre-study, prior to each dose during Week 1- 4 (induction therapy) and otherwise as clinically indicated

(q) Part A: CD32b expression assessed centrally by blood, bone marrow sample and/or lymph node sample and to be sent during screening assessments. For Part B: CD32b positivity to be confirmed during pre-screening.

8 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

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

Sample collection schemes or imaging time points may be reconsidered during the study based on emerging data which could include collection of more pharmacokinetic (PK) or pharmacodynamic (PD) data. Any changes to the sample collection schemes will be discussed and confirmed in the dose review meetings (Section 5.3). In event of any changes to the sampling schedule, it should be noted the total blood volume and burden of the patient will not increase.

8.1 Summary of pharmacokinetic and pharmacodynamic assessments

Table 2: Summary of pharmacokinetic and pharmacodynamic assessments.

Biomarker	Technology	Purpose of assay/Rationale	Type of sample	Patient group		Total blood volume per patient during study	Time points
ELIGIBILITY							
Part B only: CD32b Expression for eligibility, confirmation by one method required (costaining with B cell markers CD20 and/or, CD19))	Flow cytometry	To demonstrate target expression at tumour site for eligibility.	Whole blood and/or Bone marrow aspirate	Every patient must have CD32bpositivity confirmed	Performed alongside analysis of recent archival biopsy sample CD32b positivity will be checked first in blood and if not positive then in bone marrow.**	2 mL blood	Within 6 months before trial entry.
	IHC	To demonstrate target expression at tumour site for eligibility.	Lymph node biopsy*		Patients for whom archival lymph node biopsy is available and taken within the past 6 months OR those where recent archival sample is **not** available and whom do not test positive for CD32b in blood and bone marrow samples.**		Within 6 months before trial entry.
CD20 Expression for eligibility for patients receiving rituximab (confirmation by one method required)	Flow cytometry,	To demonstrate target expression at tumour site for eligibility.	Whole blood and/or Bone marrow aspirate	Patients who are to receive rituximab	CD20 test by flow cytometry as per routine assessment at each NHS site or central confirmation if local assessment is not available.**	2 mL blood	In patients that are refractory to rituximab, i.e either progressing whilst on rituximab based therapy (induction or maintenance) or progressing within 6 months of their last dose of rituximab, a biopsy should be performed prior to study entry to ensure that there is continued expression of CD20.
	IHC	To demonstrate target expression at tumour site for eligibility.	Lymph node biopsy*		CD20 test by IHC as per routine assessment at each site or central confirmation if local assessment is not available.		

Biomarker	Technology	Purpose of assay/Rationale	Type of sample	Patient group	Total blood volume per patient during study	Time points

**In exceptional circumstances, immunohistochemistry (IHC) analysis for CD32b (and CD20 if required) may be performed on other archival biopsies that show primary disease, however this must be discussed and agreed with the Sponsor before sample can be sent for CD32b (and CD20 if required) analysis.*

***For CD20/CD32b testing, patients with follicular lymphoma and any other patient group where B cells are not present in the circulation, blood samples should not be provided, only tissue e.g. lymph node, bone marrow or any other secondary tumour sample.*

Biomarker	Technology	Purpose of assay/Rationale	Type of sample	Patient group	Total blood volume per patient during study	Time points
SECONDARY ENDPOINTS						
Pharmacokinetics of BI-1206	ELISA	To determine the pharmacokinetic (PK) profile	Blood (Serum)	All	144 mL (Weeks 1 to 4) + up to 36mL (maintenance) = up to 180 mL	**Part A, Arm 1- Cohort 1 - Intra patient dose escalation patients only:** Pre-infusion, End of infusion, 4 hours, 24 hours, 48 hours and 72 hours post end of infusion for each BI-1206 administration in Weeks 1-4. Prior to each infusion in maintenance period.
					84 mL (Weeks 1 to 4) + up to 36 mL (maintenance) = up to 120 mL	**Part A, Arm 1- All other cohorts:** Pre- infusion, end of infusion and 4 hours, 24 hours, 48 hours and 72 hours post end of infusion following doses at Weeks 1 and 4. Prior to each infusion at Weeks 2 and 3 and also in maintenance period.
					24 mL (Weeks 1 to 4) + up to 36 mL (maintenance) = up to 60mL	**Part B, Arm 1; single-agent BI-1206 expansion:** prior to each infusion in Weeks 1 to 4 and maintenance period.
					72 mL (Weeks 1 to 4) + up to 36 mL (maintenance) = up to 108 mL	**Part A & B, Arm 2; combination-agent BI-1206:** Week 1: Pre- BI-1206 infusion, end of BI-1206 infusion, 4, 24 and 72 hours post BI-1206 infusion. Week 2 & 3: Pre- BI-1206 infusion. Week 4: Pre- BI-1206 infusion, end of BI-1206 infusion, 4, 24 and 72 hours post BI-1206 infusion. Maintenance period: prior to each infusion.

Biomarker	Technology	Purpose of assay/Rationale	Type of sample	Patient group	Total blood volume per patient during study	Time points
Anti-drug antibody (ADA)	ELISA	To assess the immunogenicity of BI-1206	Blood (serum)	All (Arm 1 and Arm 2)	up to 60 mL (18 mL in Induction period, 36 mL in maintenance, 6mL Off study)	Screening/pre-dose at Week 1, Week 5, Week 8, prior to each dose in the maintenance phase and at the off-study visit.
B-lymphocyte levels CD19	Part of Haematology assessment at NHS sites (usually part of TBNK or lymphocyte subset panel)	To evaluate the effect of BI-1206 on the depletion of peripheral blood B lymphocytes	As specified by each site.	All (Arm 1 and Arm 2)	(same sample as safety haematology assessments at each visit)	At each haematology assessment on study.
TERTIARY ENDPOINTS						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Biomarker	Technology	Purpose of assay/Rationale	Type of sample	Patient group	Total blood volume per patient during study	Time points
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Biomarker	Technology	Purpose of assay/Rationale	Type of sample	Patient group	Total blood volume per patient during study	Time points
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.2 Primary assessments

8.2.1 CD32b expression for eligibility (Part B only)

In order to be eligible for treatment on this study, patients in Part B must have confirmed CD32b positive malignancy (Table 6). Analysis of CD32b expression will be performed centrally according to agreed standard operating procedures (SOPs) and validated methods as follows;

A. For all patients:

a. If an archival lymph node biopsy is available that has been taken within 6 months of study entry this can be used for assessment of CD32b expression. Or if a lymph node biopsy is to be taken as part of routine care (not for trial purposes) within 6 months of study entry and patient consents to screen CD32b on this sample, this can be used for assessment of CD32b expression

b. Alongside this assessment, 2mL of blood may also collected within 6 months of study entry. Flow cytometry analysis will be performed for CD32b expression on B cells.

B. If no CD32b expression is noted in the blood or archival sample,

a. A bone marrow sample will be collected within 6 months of study entry (consent to main study required). A flow cytometry analysis will be performed to confirm CD32b expression on B cells. If no expression seen then and if appropriate ;

b. A lymph node biopsy may be taken within 6 months of study entry (consent to main study required, if for trial purposes only). Immunohistochemistry (IHC) will be performed for CD32b and CD20.

If no CD32b expression is noted in any of the methods above, the patient is not eligible for the trial and should be documented as a screen failure.

8.2.2 CD20 expression for eligibility (combination arm: Part A & B, Arm 2)

In order to be eligible for treatment on the combination arm of the study, patients must have confirmed CD20 positive malignancy. Analysis of CD20 expression will be performed by IHC or flow cytometry as per routine assessment at each site or confirmed centrally if the local assessment is not available.

In patients that are refractory to rituximab, i.e either progressing whilst on rituximab based therapy (induction or maintenance) or progressing within 6 months of their last dose of rituximab, a biopsy should be performed prior to study entry to ensure that there is continued expression of CD20. (Table 6).

8.3 Secondary assessments

8.3.1 BI-1206 Pharmacokinetics

BI-1206 levels will be measured in serum by enzyme-linked immunosorbent assay (ELISA) according to agreed SOPs and validated methods.

The serum concentration/time data will be analysed using non-compartmental methods. The pharmacokinetic (PK) parameters to be determined for BI-1206 include the maximum observed serum concentration (C_{max}), time to reach C_{max} (T_{max}), and the area under the serum concentration time curve (AUC), and the terminal elimination half-life ($T_{1/2}$), mean residence time (MRT), total body clearance (CLT) and steady/state volume of distribution (V_{SS}).

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

8.3.1.1 Pharmacokinetic sampling, Part A, Arm 1 single agent BI-1206

During intra-patient dose escalation (one patient): a 6 mL blood sample will be taken pre-infusion, at end of infusion (EOI) (+5 mins) and at 4 hours (±15 mins), 24 hours (±1 hour), 48 hours (±1 hour) and 72 hours (±5 hours) post the end of infusion for every BI-1206 administration during induction therapy.

From Cohort 2 onwards (Part A, Arm 1): a 6 mL blood sample will be taken pre- infusion, at end of infusion (+5 mins) and at 4 hours (±15 mins), 24 hours (±1 hour), 48 hours (±1 hour) and 72 hours (±5 hours) post end of infusion following dose 1 (Week 1) and then again at the same time points prior to and following the patient's fourth dose (Week 4). A 6 mL blood sample will also be taken prior to the BI-1206 infusions at Weeks 2 and 3 (Table 3).

The approximate volume of blood withdrawn from each patient receiving BI-1206 alone for pharmacokinetic analysis will be 84-144 mL during the induction period (8 weeks) with an additional 36 mL withdrawn over the subsequent maintenance treatment period.

All patients who receive maintenance therapy will have 6 mL blood samples taken prior to each infusion (every 8 weeks).

Table 3: Part A, Arm 1 PK sampling schedule

Time	Part A: Cohort 1 (Intra-patient dose escalation)					Part A : From Cohort 2 onwards				
	Induction				Maintenance	Induction				Maintenance
	Week 1	Week 2	Week 3	Week 4	Every 8 weeks	Week 1	Week 2	Week 3	Week 4	Every 8 weeks
Pre	X	X	X	X	X	X	X	X	X	X
EOI	X	X	X	X		X			X	
+4hrs	X	X	X	X		X			X	
+ 24hrs	X	X	X	X		X			X	
+48hrs	X	X	X	X		X			X	
+ 72hrs	X	X	X	X		X			X	
Total per patient (mL)	144				(up to 36)	84				(up to 36)

For **split dosing administration** of single agent BI-1206:

- **Part A: Cohort 2 onwards**: up to 18 PK time points may be taken during the induction period (8 weeks) with an additional 6 PK timepoints thereafter (to include pre-infusion sampling during the maintenance phase). This will be approximately 108 mLs taken over the first eight weeks with approximately 36mLs taken post the induction phase, throughout the maintenance phase.

- If split dosing is implemented, the blood volume requested will not exceed the maximum volume noted above i.e. 144 mL.

- Please refer to the study laboratory manual for handling, adjusted sample times, sample volume per time point, storage and shipment of samples.

8.3.1.2 Pharmacokinetic sampling, Part B

For patients **in Part B Arm 1 (single agent expansion):** a 6 mL blood sample will be taken each week prior to the BI-1206 infusion (every 8 weeks during the maintenance period). The approximate volume of blood withdrawn from each patient in the Part B expansion (BI-1206 analysis) will be 24 mL during the induction period with an additional 36 mL withdrawn over the subsequent maintenance treatment period (Table 4).

Table 4: Part B Arm 1, single agent expansion PK sampling schedule

Time	Induction Phase	Maintenance Phase

	Week 1	Week 2	Week 3	Week 4	Every 8 weeks
Pre	X	X	X	X	X
Total (mL)	24				(up to 36)

8.3.1.3 Pharmacokinetic sampling, Part A & B, Arm 2 (BI-1206 plus rituximab)

For patients receiving **combination therapy with BI-1206 and rituximab in the Part B Arm 2 expansion:** a 6 mL blood sample will be taken pre- BI-1206 infusion, at the end of the BI-1206 infusion (+5 mins), 4 hours after the end of the BI-1206 infusion (±15 mins), at 24 hours after the BI-1206 infusion (before the rituximab infusion) and at 72 hours after the BI-1206 infusion at Week 1. Samples will also be taken pre- BI-1206 infusion at Weeks 2 and 3. At Week 4, samples will be taken prior to the BI-1206 infusion, at the end of the BI-1206 infusion, 4 hours after the BI-1206 infusion (or if rituximab is given on the same day, at the end of rituximab infusion), at 24 hours after the BI-1206 infusion (before the rituximab infusion) and at 72 hours after the BI-1206 infusion. During the maintenance period, a sample will be taken prior to each BI-1206 infusion. The approximate volume of blood withdrawn from each patient in the Part B expansion be 72 mL during the induction period with an additional 36 mL withdrawn over the subsequent maintenance treatment period (Table 5).

Table 5: Parts A & B Arm 2, combination PK sampling schedule

Time	Induction				Maintenance
	Week 1	Week 2	Week 3	Week 4	Every 8 weeks
Pre	X	X	X	X	X
EOI (BI-1206)	X			X	
+ 4hrs (BI-1206)	X			X ^	
+ 24hrs (BI-1206)	X			X	
+72hrs (BI-1206)	X			X	
Total (mL)	72				(up to 36)

^ If rituximab is given on Day 1, this sample will be at the end of rituximab infusion instead

For **split dosing administration of BI-1206 plus rituximab**:

- Up to 18 PK time points may be taken during the induction period (8 weeks) with an additional 6 PK timepoints thereafter (to include pre-infusion sampling during the maintenance phase). This will be approximately 108 mLs taken over the first eight weeks with approximately 36mLs taken post the induction phase, throughout the maintenance phase.
- If split dosing is implemented, the blood volume requested may increase from 72 mL to 108 mL, over the first eight weeks.
- Please refer to the study laboratory manual for handling, adjusted sample times, sample volume per time point, storage and shipment of samples.

8.3.2 B-lymphocyte Levels - Pharmacodynamic

CD19 B-lymphocyte levels will be assessed and reported at each site as part of the required haematology assessment. Additionally, the assessment of the phenotype of peripheral blood and bone marrow aspirates will be performed as outlined in Section 8.4.2.

8.3.3 Detection of anti-BI-1206 antibodies

Pre-treatment, on-treatment, and post-treatment blood samples will be analysed for anti-drug antibodies (ADAs) as a batch at the end of Part A, or earlier if clinically indicated. Samples from Part B will be analysed if clinically indicated or for publication purposes (samples may not be analysed, for example if the study terminates early for safety or other reasons).

Measurement of anti-BI-1206 antibodies in serum will be performed to highlight any potential for immunogenicity and to understand the underlying reasons for any potential atypical PK. Analysis will be performed by ELISA, according to agreed SOPs and validated methods.

A 6 mL sample of blood will be collected from all patients (Parts A & B) at the following time points: Prior to first dose of BI-1206 at Week 1, Week 5, Week 8, every 8 weeks during the maintenance phase and at the off-study visit.

The approximate volume of blood withdrawn from each patient for this analysis will be 60 mL, 36 mL of which would be taken in the 1 year maintenance period (plus one 6 mL off study sample).

Table 6: Pharmacodynamic sampling schedule

Assay	Screening	Induction Phase									Maintenance Phase		Blood vol per sample (mL)	Max Total blood vol (mL)
		Pre-dose Week 1	^ wk 1 day 2 and day 4	Pre-dose Week 2	^ wk 2 day 2 and day 4	Pre-dose Week 3	^ wk 3 day 2 and day 4	Pre-dose Week 4	^ wk 4 day 2 and day 4	Week 5	Week 8	8-weekly visits	Off-study		
CD32b (Expression/Eligibility)	**X**													**2**	**2**
CD20 (Rituximab Eligibility) See Section 8.2.2.	**X**													**2**	**2**
Secondary endpoints															
CD19 B-lymphocyte levels (blood) #	Refer to Schedule of Events, Section 7.6 (Haematology time points)														
BI-1206 ADA (blood)* #		X								X	X	X	X	**6**	**60**
Tertiary endpoints															
[redacted]															

[redacted]

* Also pre each infusion during maintenance phase, and at off study. Decision to analyse or not to be made based on PK data.

These blood samples need to be taken prior to the first dose of BI-1206, they may be taken either during the screening period or prior to the BI-1206 dose at Week 1 of treatment. [redacted]

8.4 Tertiary/research assessments

[redacted]

[redacted]

8.5 Storage and Shipment of Samples

Blood, bone marrow 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.

Refer to Study Laboratory Manual for further details.

9 ASSESSMENT OF SAFETY

9.1 Investigator Responsibilities

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

9.2 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 GP). 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.

9.3 Adverse event definitions

9.3.1 Adverse event

An adverse event (AE) is any untoward, undesired or unplanned medical occurrence in a patient administered an investigational medicinal product (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.

9.3.2 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 a blood transfusions (Section 9.7.1);
- 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 brochospasm (a serious problem with breathing) requiring treatment in an emergency room,

serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalisation. The development of drug dependence or drug abuse would also be examples of important medical events.

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 *(any dose above that specified in the protocol, not necessarily intentional)*, with or without an AE.
- 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.

9.3.3 Suspected, unexpected, serious adverse reactions

A SUSAR is a suspected, unexpected, serious adverse reaction. All AEs and SAEs will be assessed by Cancer Research UK's Centre for Drug Development (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).

9.4 Determining adverse event causality

The relationship of an AE to BI-1206 and/or rituximab 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?

9.5 Expectedness

Assessment of expectedness for BI-1206 will be made by the Pharmacovigilance Department against the current version of the Investigator's Brochure (IB).

Assessment of expectedness for rituximab will be made by the Pharmacovigilance Department against the current version of the SmPC submitted as part of the IB Package.

9.6 Collection of safety information

9.6.1 Pre-Screening (Part B only)

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

9.6.2 Screening failures

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

9.6.3 Eligible patients

For eligible patients, SAE and AE collection and monitoring will commence at the time the patient gives their written consent to participate in the trial by signing the main study consent form and will continue until 125 days after the last administration of BI-1206 and/or rituximab on study (whichever is later) or until the patient starts another anti-cancer therapy.

Should an Investigator become aware of any drug-related SAEs after this 125 day period (even if the patient has started another anti-cancer therapy), these must also be reported to the CDD within the expedited timelines in Section 9.7.

9.6.4 Follow-up of AEs and SAEs

Follow-up of 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.

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.

9.6.5 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
- Occupational exposure *(to a person other than the patient, for example spilling of IMP on hands of nurse or splashing in the eye)*

Any occurrences of these should be reported in the same manner as SAEs (Section 9.7).

9.7 Reporting of SAEs to the Pharmacovigilance Department, CDD

All SAEs and safety information of interest as defined in Section 9.6.5, 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 e-mailed 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 the severity of 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 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 PV Department within the specified timelines specified above.

9.7.1 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 electronic case report form (eCRF).

Prolongation of hospitalisation - Prolongation of hospitalisation without an associated adverse event (for example, prolonged hospitalisation while appropriate social care is set up for elderly patients).

Admission for monitoring in patients at risk of tumour lysis syndrome - Where a patient has a high disease burden and is at greater risk of tumour lysis syndrome it may be appropriate to admit them for additional monitoring following IMP administration. Where this additional monitoring is planned prior to starting the infusion, this is exempt from being reported as an SAE.

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.

9.8 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.

9.9 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]

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.

9.10 Pregnancy

Female patients who become pregnant during the treatment period 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 twelve months afterwards. This should be done as part of the consent process by explaining clearly to the patient the potential dangers of becoming pregnant and also providing each patient with information about appropriate medically approved contraception. Two forms of medically approved contraception should be used, such as:

- oral contraceptives and condom;
- 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 twelve months after completing the trial.

Alternatively the patient may agree to sexual abstinence, effective from main study consent throughout the trial and for twelve 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 the patient 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 the BI-1206 and in Arm 2, rituximab.

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 twelve 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 Notification 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 should document within the patient notes, the patient confirming consent for the Sponsor to collect pregnancy follow-up information. In the case that the partner of a patient becomes pregnant, a consent form should be provided to the patient's partner in order to obtain consent for collecting privacy data, in accordance with the general data protection regulation.

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 twelve 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.

10 ASSESSMENT OF EFFICACY

10.1 Measurement of disease

Disease in patients with CLL must be measured according to the Hallek, 2008 criteria given in Appendix 4 [42]. For patients with lymphomas, disease must be measured according to the Cheson 2014 criteria given in Appendix 5 [43] and for those with Waldenström's macroglobulinemia, disease must be assessable by the criteria stated in Appendix 6 [44]

10.2 Definition of clinical benefit

The determination of clinical benefit will normally require the patient to have achieved a minimum response of stable disease according to the response criteria defined in Appendices 4, 5 and 6 ([42], [43], [44]). In the exceptional event of an investigator considering that a patient is deriving clinical benefit despite failure to achieve stable disease or better, the case must be discussed with the CI and Sponsor who must agree to continuation of maintenance treatment before any such treatment will commence.

10.3 Timing and type of tumour assessments

A thorough evaluation of malignancy, as judged appropriate by the Investigator, and in line with the protocol, must be performed before a patient receives their first dose of BI-1206 or rituximab. The same methods that detect evaluable lesions at baseline must be used to follow these lesions throughout the trial. To ensure compatibility, 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 with BI-1206 or rituximab. 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 performed within **one** week prior to a patient's first dose of BI-1206.

Copies of the scans must be available for external independent review if requested by Cancer Research UK's Centre for Drug Development (CDD).

All patients will be evaluated at baseline, four weeks after the last dose of BI-1206 or rituximab on study, every 16 weeks (± 2 weeks) during their maintenance phase and at off-study, unless progression occurs at an earlier time point, at which the patient will be evaluated instead.

10.3.1 Tumour assessment for CLL patients

For patients with CLL, tumour assessments will include:

Baseline (within 28 days prior to induction therapy Week 1)

- Physical examination and measurement of clinical/palpable lesions.
- CT scan of neck, chest, abdomen and pelvis.
- Peripheral blood sample for measurement of B lymphocytes, neutrophils, platelets and haemoglobin.
- Bone marrow aspirate (can be performed within eight weeks of induction therapy, Week 1 and may have been performed as part of standard care – see Section 7.1.2).
- 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.

Evaluations at Week 8 (4 Weeks post last BI-1206 induction therapy administration)

- Physical examination and measurement of clinical/palpable lesions.
- CT scan of neck, chest, abdomen and pelvis.
- Peripheral blood sample for measurement of B lymphocytes, neutrophils, platelets and haemoglobin.
- Bone marrow aspirate for patients who had a positive test at baseline and who have shown a complete response (at least two months after last dose of study medication).

± one week window may be acceptable for the Week 8 scans due to logistical reasons however every effort should be made to keep to the 8 week specified time point. Please notify CI and Sponsor if scans cannot be performed at Week 8.

Evaluations every 16 weeks (± 2 weeks) during maintenance phase

Patients who have not shown disease progression at an earlier assessment will have the following assessments performed:

- Physical examination and measurement of palpable lesions.
- CT scan of neck chest, abdomen and pelvis.
- Peripheral blood sample for measurement of B lymphocytes, neutrophils, platelets and haemoglobin.
- Bone marrow aspirate for patients who have shown a complete response and who have not had prior bone marrow confirmation of response.

Evaluations at off-study

Patients who have not shown disease progression at an earlier assessment (or if in the maintenance phase have not had an assessment within the previous 8 weeks) will have the following assessments performed:

- Physical examination and measurement of palpable lesions.
- CT scan of neck, chest, abdomen and pelvis.
- Peripheral blood sample for measurement of B lymphocytes, neutrophils, platelets and haemoglobin.
- Bone marrow aspirate and biopsy for patients who had a positive test at baseline and who have shown a complete response and who have not had prior bone marrow confirmation of response.

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 Hallek criteria (Appendix 5).

10.3.2 Tumour assessments for patients with lymphomas (other than Waldenström's macroglobulinemia)

For patients with lymphomas, tumour assessments will include:

Baseline (within 28 days of induction therapy Week 1)

- Physical examination and measurement of clinical/palpable lesions.
- CT scan of neck, chest, abdomen and pelvis.
- [^{18}F]FDG-PET scan (for PET-avid lymphomas only) according to the Deauville scale criteria as described in Appendix 2. Bone marrow aspirate (can be performed within eight weeks of induction therapy Week 1 and may have been performed as part of standard care – see Section 7.1.2).

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.

Evaluations at Week 8 (4 Weeks post last BI-1206 administration)

- Physical examination and measurement of clinical/palpable lesions.
- CT scan of neck, chest, abdomen and pelvis.
- [^{18}F]FDG-PET scan (if positive at baseline according to the Deauville scale criteria set out below).
- Bone marrow aspirate for patients who had a positive test at baseline and who have shown a complete response.

± one week window may be acceptable for the Week 8 scans due to logistical reasons however every effort should be made to keep to the 8 week specified time point. Please notify CI and Sponsor if scans cannot be performed at Week 8.

Evaluations every 16 weeks (± 2 weeks) during maintenance phase

Patients who have not shown disease progression at an earlier assessment will have the following assessments performed:

- Physical examination and measurement of clinical/palpable lesions.
- CT scan of neck, chest, abdomen and pelvis.
- If a complete response is noted on the above assessments, then [^{18}F]FDG-PET scan should be performed (if positive at baseline).
- Bone marrow aspirate for patients who had a positive test at baseline and who have shown a complete response and who have not had prior bone marrow confirmation of response.

Evaluations at off-study

Patients who have not shown disease progression at an earlier assessment (or if in the maintenance phase have not had an assessment within the previous 8 weeks) will have the following assessments performed:

- Physical examination and measurement of palpable lesions.
- CT scan of neck, chest, abdomen and pelvis.
- If a complete response is noted on the above assessments, then [^{18}F]FDG-PET scan should be performed (if positive at baseline).

- Bone marrow aspirate for patients who had a positive test at baseline, who have shown a complete response and who have not had prior bone marrow confirmation of response.

10.3.3 Tumour assessments for patients with Waldenström's macroglobulinaemia

For patients with Waldenström's macroglobulinaemia (WM), tumour assessments will include:

Baseline (within 28 days of induction therapy Week 1)

- Physical examination and measurement of clinical/palpable lesions.
- CT scan of neck, chest, abdomen and pelvis.
- [^{18}F]FDG-PET scan where there is a concern regarding high grade transformation
- Bone marrow aspirate (can be performed within eight weeks of induction therapy Week 1 and may have been performed as part of standard care – see Section 7.1.2).
- A blood sample should be taken for assessment of serum paraprotein by electrophoresis and immunofixation. Please note, this serum paraprotein is also sometimes referred to as serum monoclonal protein IgM, but should not be confused with IgM assessed as part of the immunoglobulin sample also described in Section 7.1.2 as this is a different assessment. Normal serum IgM levels should also be measured.

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.

Evaluations at Week 8 (4 Weeks post last BI-1206 administration)

- Physical examination and measurement of clinical/palpable lesions.
- CT scan of neck, chest, abdomen and pelvis.
- Bone marrow aspirate for patients who had a positive test at baseline and who have shown a complete response.
- A blood sample should be taken for assessment of serum paraprotein. Normal serum IgM levels should also be measured.

± one week window may be acceptable for the Week 8 scans due to logistical reasons however every effort should be made to keep to the 8 week specified time point. Please notify CI and Sponsor if scans cannot be performed at Week 8.

Evaluations every 16 weeks (± 2 weeks) during maintenance phase

Patients who have not shown disease progression at an earlier assessment will have the following assessments performed:

- Physical examination and measurement of clinical/palpable lesions.
- CT scan of neck, chest, abdomen and pelvis.
- Bone marrow aspirate for patients who had a positive test at baseline and who have shown a complete response and who have not had prior bone marrow confirmation of response.
- A blood sample should be taken for assessment of serum paraprotein. Normal serum IgM levels should also be measured.

Evaluations at off-study

Patients who have not shown disease progression at an earlier assessment (or if in the maintenance phase have not had an assessment within the previous 8 weeks) will have the following assessments performed:

- Physical examination and measurement of palpable lesions

- CT scan of neck, chest, abdomen and pelvis
- Bone marrow aspirate for patients who had a positive test at baseline, who have shown a complete response and who have not had prior bone marrow confirmation of response
- A blood sample should be taken for assessment of serum paraprotein. Normal serum IgM levels should also be measured.

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.

[^{18}F]FDG-PET scans will be assessed according to the Deauville criteria five point scale [45], as detailed in Appendix 2 (Section 16.2). Lesions which correspond to 1 to 3 on the Deauville scale will be considered PET negative for this study, lesions which correspond to 4 to 5 on the Deauville scale will be considered as PET positive.

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 Cheson criteria (Appendix 5).

10.4 Tumour response

All patients who meet the eligibility criteria receive at least one dose of mAb (BI-1206 with/without rituximab) as part of this trial and who have a baseline assessment of disease and at least one repeat assessment will be evaluable for response. Best tumour response will be assessed and reported in line with the efficacy endpoints for the trial.

Expert reviewers appointed by CDD may undertake an independent review of Investigator assessed tumour responses. The expert reviewers will include at least one specialist who is not an Investigator in the trial. In case of disagreement between the Investigator and the expert reviewers' assessment, the Investigator will be informed of the expert reviewers' assessment and both assessments reported in the clinical study report (CSR). The eCRF will reflect the Investigator's opinion.

The following categories of response will be defined, in accordance with the categories outlined in Appendices 4, 5 and 6 respectively

10.4.1 Response categories for CLL patients

Complete Response (CR)

Complete Response (with incomplete marrow recovery) (CRi)

Partial Remission (PR)

Stable Disease (SD)

Progressive Disease (PD)

10.4.2 Response categories for lymphoma patients (except those with Waldenström's macroglobulinaemia)

Complete Remission (CR)

Partial Remission (PR)

Stable Disease (SD)

Progressive Disease (PD)

10.4.3 Response categories for Waldenström's macroglobulinaemia patients

Complete Response (CR)
Very Good Partial Response (VGPR)
Partial Response (PR)
Minor Response (MR)
Stable Disease (SD)
Progressive Disease (PD)

10.4.4 Recording of response in the eCRF

The applicable overall response category for each visit that includes disease assessment must be recorded in the eCRF.

11 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 4 weeks post the last BI-1206 administration in the induction phase). However, if the Investigator removes a patient from the trial or if the patient declines further participation, final 'off-study' assessments should be performed ideally before any subsequent 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 electronic case report form (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 study treatment. Every effort will be made to complete safety follow-up activities unless consent to safety follow-up has been withdrawn by the patient.

- Adverse event/serious adverse event (AE/SAE);
- Withdrawal of consent;
- Serious deviation from 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 BI-1206 or rituximab.
- Evidence of disease progression;
- Pregnancy (for female patients during the study).

12 DEFINING THE END OF TRIAL

The ‘end of trial’ is defined as the date when:

> The last patient has received their last maintenance treatment, completed their off study visit, and follow up period for related AEs (if appliciable) and 1 year survival follow up has been completed for all patients.

It is the responsibility of the CDD to inform the Medicines and Healthcare products Regulatory 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.

Recruitment will cease when:

- The study drug (s) is/are considered too toxic to continue treatment before the required number of patients have been recruited.
- The stated number of patients to be recruited has been reached.
- The stated objectives of the trial are achieved.

Regardless of the reason for termination, all data available for patients 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.

13 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

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

- The trial is terminated early
- The end of trial as defined in Section 12 has been reached.

13.1 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 deviations, 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.

13.2 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 (AEs) will be reported for each dose level and presented as tables of frequency of AEs by body system and by worst severity grade observed. Tables should indicate related and unrelated events.

13.3 Pharmacokinetics

The serum concentration/time data will be analysed using non-compartmental methods. The pharmacokinetic (PK) parameters to be determined for BI-1206 include the maximum observed serum concentration (C_{max}), time to reach C_{max} (T_{max}), and the area under the serum concentration time curve (AUC), and the terminal elimination half-life ($T_{1/2}$), total body clearance (CLT) and steady/state volume of distribution (V_{SS}).

13.4 Pharmacodynamics

The pharmacodynamic analyses to be performed are described below. Reports will undergo a quality control (QC) step prior to finalisation and will be signed by the person responsible for performing the assays and the laboratory Quality Assurance (QA) manager once final.

Anti-drug antibody (ADA)

The presence of anti-BI-1206-antibody responses will be assessed using ELISA and reported per patient.

B-lymphocyte levels: CD19, CD20 and CD32b

CD19 B-lymphocyte levels will be assessed and reported at each site as part of the regular haematology assessment to determine the level of peripheral blood B-lymphocyte depletion. Results will be entered onto the clinical database and provided to the analysing pharmacodynamic laboratory for comment.

CD32b and CD20/CD19 B-lymphocyte expression levels in blood will be measured using flow cytometry. Results will be reported and analysed longitudinally for each patient.

Levels of B lymphocytes will be measured in bone marrow aspirate to determine the level of bone marrow B lymphocyte depletion. Cell surface markers will be assessed using flow cytometry and results analysed longitudinally for each patient.

[redacted]

13.5 Anti-tumour activity

Documenting anti-tumour activity is a secondary objective of this trial. Patients must receive at least one dose of BI-1206 and/or rituximab on as part of this trial; have a baseline disease assessment and at least one follow-up disease assessment to be evaluable for response. Patients who experience clear clinical disease progression without formal post-treatment disease assessment will be included and will be considered to have progressive disease. 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.

13.6 Overall Survival and Progression-Free Survival

13.6.1 Overall Survival

All patients who receive BI-1206 and/or rituximab on as part of this trial will be evaluable for overall survival, regardless of whether they subsequently receive other anti-cancer treatments. Overall survival will be measured from the date of administration of the first dose of BI-1206 on this trial. Subgroup analyses of per protocol patients may be performed. Median overall survival will be reported. Patients who are lost to follow-up will be censored at the time of last contact, patients who start a new treatment will not be censored.

13.6.2 Progression-Free Survival

All patients who receive BI-1206 and/or rituximab as part of this study and who complete a baseline and at least one post-treatment disease assessment (or experience clear disease progression without a formal post-treatment disease assessment) will be evaluable for progression-free survival (PFS), regardless of whether they subsequently receive other anti-cancer treatments. PFS will be measured from the date of administration of the first dose of BI-1206. Subgroup analyses of per protocol patients may be performed. Median progression free survival will be reported. Patients who are lost to follow-up will be censored at the time of last recorded disease assessment, patients who start a new treatment will not be censored.

14 ADMINISTRATION

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

14.1 Protocol deviations and amendments

The protocol should be adhered to throughout the conduct of the study, if a situation arises where the conduct of the study may not be in line with the protocol, then site should contact the CDD to discuss this.

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, Health Research Authority (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.

14.2 Serious breach of Good Clinical Practice

A serious breach is a breach which is likely to effect to a significant degree: the safety or physical or mental integrity of the subjects of the trial, or the scientific value of the trial.

In order that the Sponsor can fulfil their obligations in terms of reporting serious breaches of Good Clinical Practice (GCP) to the MHRA within seven calendar days of identification, site staff must inform the Sponsor of any unplanned deviations to the trial protocol (or GCP principles) as soon as possible after the deviation occurs to allow prompt evaluation by the Sponsor.

14.3 Completion of the electronic case report form

Electronic case report forms (eCRFs) approved and maintained 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 list 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.

The collection and processing of personal data from the patients enrolled in this clinical trial will be limited to those data that are necessary to investigate the efficacy, safety, quality and usefulness of the study drug used in this trial. The data must be collected and processed with adequate precautions to ensure patient confidentiality and compliance with applicable data privacy protection according to the applicable regulations.The data collected will comply with Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data.

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.

14.4 Trial performance, monitoring, auditing and inspection

Before the trial can be initiated, the prerequisites for conducting the trial must be clarified and the organisational preparations made with the trial centre. The 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) will be responsible for monitoring data quality in accordance with CDD's standard operating procedures (SOPs). A strategic monitoring approach, including targeted source data verification, will be implemented where appropriate.

Before the study 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.

At the end of the trial all unused BI-1206 supplied must be destroyed at site (only once authorised to do so by the CRA or CSM) or if authorised by Cancer Research UK returned to the supplier.

It is the responsibility of the Sponsor to notify the REC of the 'end of the trial'. (see definition in Section 12).

During the course of the trial, the Quality Assurance Department of the CDD, or external auditors contracted by the CDD, may conduct an on-site audit visit (ICH Topic E6 (R2) Guideline for Good Clinical Practice Sections 1.6).

Principal Investigators conducting this trial will accept the potential for inspection by the MHRA.

14.5 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.

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, NHS Trust staff and by regulatory authorities. Details will remain confidential and patients' names will not be recorded outside the hospital.

14.6 Clinical study report

At appropriate intervals, interim data listings will be prepared to give the Investigator the possibility to review the data and check the completeness of information collected. All clinical data will be presented at the end of the trial on final data listings. The Sponsor will prepare a clinical study report (CSR) based on the final data listings. The CSR 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 Research Ethics Committee.

14.7 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 serious adverse event (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.

14.8 Ethical considerations

Before starting the trial, the protocol and patient informed consent document(s) (ICD) must go through the CDD's external review process, and be approved by the CDD's Protocol and Safety Review Board (PSRB) and receive the favourable opinion of the assigned REC.

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 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.

14.9 Indemnity

This trial is sponsored by 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.

14.10 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 the CDD at least 42 days in advance of being submitted for publication to allow time for the CDD to schedule a review and resolve any outstanding issues. Abstracts, presentations and press releases must be submitted to the 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 Chief Investigator should be the principal author of the paper reporting the trial results, and any Investigator recruiting ≥ 10% of patients should be listed as an author - in order of numbers of patients recruited.

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

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16 APPENDICES

16.1 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

16.2 APPENDIX 2: DEAUVILLE CRITERIA FIVE POINT SCALE FOR FDG-PET REPORTING

Below is an extract from M. Meignan, A. Gallamini, and C. Haioun, “Report on the first international workshop on interim-PET-scan in lymphoma,” Leukemia & Lymphoma, vol. 50, no. 8, pp. 1257–1260, 2009.

Five points scale

1. No uptake
2. Uptake less than mediastinum
3. Uptake more than mediastinum but less than liver
4. Uptake moderately increased above liver at any site
5. Markedly increased uptake at any site including new sites of disease

16.3 APPENDIX 3: NEW YORK HEART ASSOCIATION (NYHA) SCALE

Class I – patients with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue dyspnoea (or fatigue, palpitation or anginal pain)

Class II – patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity results in dyspnoea (or fatigue, palpitation or anginal pain)

Class III – patients with cardiac disease resulting in marked limitations of physical activity; they are comfortable at rest; less than ordinary physical activity causes dyspnoea (or fatigue, palpitation or anginal pain)

Class IV – patients with cardiac disease resulting in inability to carry out physical activity without discomfort; symptoms of dyspnoea (or of angina) may be present even at rest; if any physical activity is undertaken, discomfort is increased.

16.4 APPENDIX 4: MEASUREMENT OF DISEASE FOR PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA

Below is an excerpt of text from Hallek *et al*; Blood *2008 111: 5446-5456*

Definition of response, relapse, and refractory disease

Assessment of response should include a careful physical examination and evaluation of the blood and marrow (Tables 3,4).

Table 3 Recommendations regarding the response assessment in CLL patients

Diagnostic test	General practice**	Clinical trial
History, physical examination††	Always	Always
Immunophenotyping of peripheral blood lymphocytes‡‡	If clinical and hematologic response indicates CR	If clinical response and hematologic response indicates CR
CBC and differential count§§	Always	Always
Marrow aspirate and biopsy¶¶	At cytopenia of uncertain cause	At CR or cytopenia of uncertain cause
Assessment for minimal residual disease‖‖	No	If a long-lasting CR is the desired endpoint
Ultrasound of the abdomen††	Possible, if previously abnormal	No
CT scans of chest, pelvis, and abdomen††	No	Indicated if previously abnormal and otherwise in CR

The section of guidelines for each table entry is indicated by symbols.

**General practice is defined as the use of accepted treatment options for a patient with CLL not enrolled in a clinical trial.

††"Absence of significant lymphadenopathy," "No hepatomegaly or splenomegaly by physical examination," "Absence of constitutional symptoms," "Reduction in lymphadenopathy," "Lymphadenopathy," "An increase in the liver or spleen size by 50% or more or the de novo appearance of hepatomegaly or splenomegaly."

‡‡"Absence of clonal lymphocytes in the peripheral blood."

§§"Blood counts above the following values," "The blood count should show one of the following results," "An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter," "Occurrence of cytopenia (neutropenia, anaemia, or thrombocytopenia) attributable to CLL."

¶¶"For patients in clinical trials (Table 3): a marrow aspirate and biopsy should be performed at least 3 months after the last treatment and if clinical and laboratory results (the first 5 points under "Complete remission") demonstrate that a CR has been achieved."

‖‖"Minimal residual disease."

5.1. Complete remission (CR)

CR requires all of the following criteria as assessed at least 2 months after completion of therapy:

5.1.1. Peripheral blood lymphocytes (evaluated by blood and differential count) below 4 x ***10^9/L (4000/μL).*** In clinical trials, the presence of minimal residual disease (MRD) after therapy should be assessed (see Section 5.9). The sensitivity of the method used to evaluate for MRD should be reported.

5.1.2. Absence of significant lymphadenopathy (e.g., lymph nodes >1.5 cm in diameter) by physical examination. In clinical trials, a CT scan of the abdomen, pelvis, and thorax is desirable if previously abnormal. Lymph nodes should not be larger than 1.5 cm in diameter.

5.1.3. No hepatomegaly or splenomegaly by physical examination. In clinical trials, a CT scan of the abdomen should be performed at response assessment if found to be abnormal before therapy or if physical examination is inconclusive at the time of evaluation.

5.1.4. Absence of constitutional symptoms.

5.1.5. Blood counts above the following values:

5.1.5.1.Neutrophils more than 1.5 x *10^9/L (1500/*µ*L) without need for exogenous growth factors.*

5.1.5.2. Platelets more than 100 x *10^9/L (100 000/*µ*L) without need for exogenous growth factors.*

5.1.5.3. Haemoglobin more than 110 g/L (11.0 g/dL) without red blood cell transfusion or need for exogenous erythropoietin.

5.1.6. For patients in clinical trials (Table 3), a marrow aspirate and biopsy should be performed at least 2 months after the last treatment and if clinical and laboratory results listed in sections 5.1.1 through 5.1.5 demonstrate that a CR has been achieved.

To define a CR, the marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. In some cases, lymphoid nodules can be found, which often reflect residual disease. These nodules should be recorded as "nodular PR." Moreover, immunohistochemistry should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than CLL cells or of CLL cells. If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, or until peripheral blood counts have recovered. However, this time interval should not exceed 6 months after the last treatment. A marrow biopsy should be compared with that of pre-treatment marrow. In general practice, the use of a marrow biopsy for evaluating a CR is at the discretion of the physician. In clinical trials aiming at maximizing the CR rate, the quality of the CR should be assessed for MRD by flow cytometry (see Section 5.9) or by immunohistochemistry (IHC).

5.1.7. A controversial issue is how best to categorize the response of patients who fulfil all the criteria for a CR (including the marrow examinations described in Section 5.16) but who have a persistent anaemia or thrombocytopenia or neutropenia apparently unrelated to CLL but related to drug toxicity.

We recommend that these patients be considered as a different category of remission: CR with incomplete marrow recovery (CRi). For the definition of this category, CRi, the marrow evaluation (see Section 5.1.6) should be performed with scrutiny and not show any clonal infiltrate. In clinical trials, CRi patients should be monitored prospectively to determine whether their outcome differs from that of patients with detectable residual disease or with noncytopenic CR.

5.2. Partial remission (PR)

PR is defined by the criteria described in Sections 5.2.1, 5.2.2, or 5.2.3 (if abnormal before therapy), as well as one or more of the features listed in Section 5.2.4. To define a PR, these parameters need to be documented for a minimal duration of 2 months (Table 4). Constitutional symptoms persisting for more than 1 month should be recorded.

5.2.1. A decrease in the number of blood lymphocytes by 50% or more from the value before therapy.

5.2.2. Reduction in lymphadenopathy (by CT scans in clinical trials or by palpation in general practice) as defined by the following:

5.2.2.1. A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy.

5.2.2.2. No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (< 2 cm), an increase of less than 25% is not considered to be significant.

5.2.3. A reduction in the noted pre-treatment enlargement of the spleen or liver by 50% or more, as detected by CT scan (in clinical trials) or palpation (in general practice).

5.2.4. The blood count should show one of the following results:

5.2.4.1. Neutrophils more than 1.5 x *10^9/L (1500/*µ*L) without need for exogenous growth factors.*

5.2.4.2. Platelet counts greater than 100 x*10^9/L (100,000/*µ*L) or 50% improvement over baseline without need for exogenous growth factors.*

5.2.4.3. Hemoglobin greater than 110 g/L (11.0 g/dL) or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin.

5.3. Progressive disease

Progressive disease during or after therapy is characterized by at least one of the following:

5.3.1. Lymphadenopathy. Progression of lymphadenopathy is often discovered by physical examination and should be recorded. In CLL, the use of CT scans usually does not add much information for the detection of progression or relapse. Therefore, the use of imaging methods to follow CLL progression is at the discretion of the treating physician. Disease progression occurs if one of the following events is observed:

Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates. An increase by 50% or more in greatest determined diameter of any previous site.

5.3.2. An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.

5.3.3. An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter.

5.3.4. Transformation to a more aggressive histology (e.g., Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.

5.3.5. Occurrence of cytopenia (neutropenia, anaemia, or thrombocytopenia) attributable to CLL.

5.3.5.1. During therapy. Cytopenias may occur as a side effect of many therapies and should be assessed according to Table 5. During therapy, cytopenias cannot be used to define disease progression. Each protocol should define the amount of drug(s) to be administered with such cytopenias.

5.3.5.2. After treatment. The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than 100 x 10^9/L (100 000cells/_L), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

5.4. Stable disease

Patients who have not achieved a CR or a PR, and who have not exhibited progressive disease, will be considered to have stable disease (which is equivalent to a non response).

5.5. Treatment failure

Responses that should be considered clinically beneficial include CR and PR; all others (e.g., stable disease, non response, progressive disease, or death from any cause) should be rated as a treatment failure.

5.6. Time to progression, progression-free survival, and overall survival

Time to progression (TTP) is defined as the time from study entry until objective disease progression (see Section 5.3). Progression free survival (PFS) is defined as the time from study entry until objective disease progression or death. Overall survival is defined as the time from study entry until death from any cause, and is measured in the intent-to-treat population.

5.7. Relapse

Relapse is defined as a patient who has previously achieved the above criteria (Sections 5.1 and 5.2) of a CR or PR, but after a period of 6 or more months, demonstrates evidence of disease progression (see Section 5.3).

5.8. Refractory disease

Refractory disease is defined as treatment failure (as defined in Section 5.5) or disease progression within 6 months to the lastantileukemic therapy. For the definition of “high-risk CLL” justifying the use of allogeneic stem cell transplantation, the disease should be refractory to a purine analog-based therapy or to autologous hematopoietic stem cell transplantation.

5.9. Minimal residual disease

The complete eradication of the leukemia is an obvious desired endpoint. New detection technologies, such as multicolour flow cytometry and real-time quantitative PCR, have determined that many patients who achieved a CR by the 1996 NCI-WG guidelines have detectable MRD. Although eradication of MRD may improve prognosis, prospective clinical trials are needed to define whether additional treatment intended solely to eradicate MRD provides a significant benefit to clinical outcome. The techniques for assessing MRD have undergone a critical evaluation and have become fairly standard.60 Either 4-color flow cytometry (MRD flow) or allele-specific oligonucleotide PCR is reliably sensitive down to a level of approximately one CLL cell in 10 000 leukocytes. As such, patients will be defined as having a clinical remission in the absence of MRD when they have blood or marrow with less than one CLL cell per 10 000 leukocytes. The blood generally can be used for making this assessment except during the period within 3 months of completing therapy, particularly for patients treated with alemtuzumab, rituximab, and other antibodies targeting CLL. In such cases, it is essential to assess the marrow for MRD. Therefore, future clinical trials that aim toward achieving long-lasting CRs should include at least one test to assess MRD because the lack of leukemia persistence using these sensitive tests seems to have a strong, positive prognostic impact.

Table 4: Response definition after treatment for patients with CLL, using the parameters of Tables 1 and and 3

Response definition after treatment for patients with CLL, using the parameters of Tables 1 and 3

Parameter	CR*	PR*	PD*
Group A			
Lymphadenopathy†	None > 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/μL	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi (5.1.6).	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B			
Platelet count	> 100000/μL	> 100000/μL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils‡	> 1500/μL	> 1500/μL or > 50% improvement over baseline	

Group A criteria define the tumor load, group B criteria define the function of the hematopoietic system (or marrow).

↵* CR (complete remission): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR (partial remission): at least two of the criteria of group A plus one of the criteria of group B have to be met; SD is absence of progressive disease (PD) and failure to achieve at least a PR; PD: at least one of the above criteria of group A or group B has to be met.

↵† Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).

↵‡ These parameters are irrelevant for some response categories.

16.5 APPENDIX 5: Criteria for disease assessment for patients with lymphoma (other than Waldenström's Macroglobulinaemia)

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.

16.6 APPENDIX 6: Criteria for disease assessment in patients with Waldenström's Macroglobulinaemia

Below is an extract from Owen et al (British Journal of Haematology, 2013, 160, 171-176) this should be used in conjunction with the previous update from Kimby et al (Clinical Lymphoma and Myeloma, Vol 6, Issue 5, pages 380–383, Mar 2006)to assess disease response in patients with WM.

Response (abbreviation)	Criteria
Complete response (CR)	Absence of serum monoclonal IgM protein by immunofixation Normal serum IgM level Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response (VGPR)	Monoclonal IgM protein is detectable ≥90% reduction in serum IgM level from baseline[a] Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Partial response (PR)	Monoclonal IgM protein is detectable ≥50% but<90% reduction in serum IgM level from baseline[a] Reduction in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Minor response (MR)	Monoclonal IgM protein is detectable ≥25% but<50% reduction in serum IgM level from baselinea No new signs or symptoms of active disease
Stable disease (SD)	Monoclonal IgM protein is detectable <25% reduction and <25% increase in serum IgM level from baselinea No progression in extramedullary disease, i.e.,lymphadenopathy/splenomegaly No new signs or symptoms of active disease
Progressive disease (PD)	≥25% increase in serum IgM level[a] from lowest nadir (requires confirmation) and/or progression in clinical features attributable the disease

[a] Sequential changes in IgM levels may be determined either by M protein quantitation by densitometry or total serum IgM quantitation by nephelometry.