IcICLLe: Assessment of the Mechanism of Action of Ibrutinib (PCI-32765) in B-cell Receptor Pathway Inhibition in Chronic Lymphocytic Leukaemia (CLL)

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SIGNATURE PAGE

IcICLLe Study Protocol Version 12.0 22-Aug-2022
This protocol has been approved by:

Name: Prof Peter Hillmen Trial Role: Chief Investigator

Signature: P. Hill Date: 20/SEP/2022

This protocol describes the IcICLLe trial and provides information about procedures for patients taking part in the IcICLLe trial. The protocol should not be used as a guide for treatment of patients not taking part in the IcICLLe trial.

AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	04-Nov-2013	2.0	Substantial	Change for MHRA; minimum age increased from 16 to 18
2	09-Dec-2013	2.0a	Non-Substantial	Update of TSC membership
3	21-Jan-2014	3.0	Substantial	Change of TSC to DMC Addition of stopping rules, Increasing age limit in treatment naive cohort Clarification of assessments Streamlining of primary outcome measures Clarification of secondary and exploratory outcomes
4	08-May-2014	4.0	Substantial	Addition to inclusion criteria to include adequate hepatic and renal function in both cohorts of patients. Exclusion criteria to exclude patients who have had major surgery within 4 weeks of registration and history of stroke or intracranial haemorrhage in both cohorts of patients. Update of safety data to reflect current numbers of patients treated. Update of assessments schedule to clarify when samples should be taken.
5	09-Jun-2015	5.0	Substantial	Addition of second registration to the IcICLLe extension study.

				Updated trial endpoints Updated safety information for ibrutinib
6	19-Aug-2015	6.0	Substantial	Updated inclusion criteria for the IcICLLe Extension Study Additional advice on monitoring patients for TLS and thrombocytopenia Change to Co-Investigators
7	05-Sep-2016	7.0	Substantial	Updated safety information for ibrutinib and obinutuzumab Clarification of trial endpoints – time frames Clarification of inclusion criteria – phenotype of CLL suitable for monitoring Clarification of cohorts for the extension study Clarification of the sample collection instructions Updated statistical analysis section Updated information on translational studies
8	18-Aug-2017	8.0	Substantial	Clarification of patient population sizes. Amendment of eligibility criteria. Inclusion of stopping rules for patients reaching MRD negative remission. Update to the safety information for ibrutinib and obinutuzumab. Clarification of the rates of obinutuzumab infusion on re-challenge following an IRR.
9	26-Jul-2018	9.0	Substantial	Update to the safety information for ibrutinib and obinutuzumab under precautions for use. Prophylaxis for *Pneumocystis Jirovecii pneumonia (PJP)* has been mandated for all patients in receipt of ibrutinib. Update to instructions on infusion rates in the absence of infusion related reactions. Confidentiality section updated to reflect the General Data Protection Regulation (GDPR) which came into effect on 25 May 2018. Update to assessments to state that central review of CT scans may be requested by the TMG. Update to sample collection instructions. No longer mandating collection of peripheral blood and first pull bone marrow aspirate films. Updates to concomitant medication section.

10	18-Jul-2019	10.0	Substantial	Addition of guidance for interpretation of HMDS MRD reports. Section 11 - Update to end of trial definition. Removal of '5 year follow-up' in end of trial definition. Patients will now followed up past 'Year 5'.
11	18-Jul-2019	10.0a	Non-substantial	CT required at progression was previously omitted from the schedule of events; this has been corrected so that the schedule of events reflects protocol requirements. Version corrected on front page of protocol.
12	24-Aug-2021	11.0	Substantial	Addition of ACE inhibitors and ARBs as prohibited concomitant medications for patients receiving ibrutinib. This change has been made as a result of an Urgent Safety Measure implemented on 20-Aug-2021 from a risk identified in the FLAIR study. In an interim analysis for FLAIR, it was identified that participants with pre-existing hypertension or cardiac co-morbidities randomised to ibrutinib + rituximab had an elevated risk of sudden unexplained death or cardiac death, which appears to be associated predominantly with ACE inhibitors. ARBs target the same pathway as ACE inhibitors so these may be considered to also be a potential risk. This was discussed with the IcICLLe Trial Management Group and, although the number of sudden or cardiac deaths noted in the FLAIR study overall was very small, it was agreed that urgent action should be taken to limit risk to trial participants receiving ibrutinib and ACE inhibitors or ARBs. ACE inhibitors and ARBs have been added to Appendix 10 – Cautioned And Prohibited Medication.
13	22-Aug-2022	12.0	Substantial	Addition of information from Other Safety Observations Section of the Ibrutinib IB regarding Cerebrovascular Accidents. Addition of further information from the Precautions and Warnings Section of the Ibrutinib IB regarding Cardiac Arrhythmias and Cardiac Failure. Update to the dose ibrutinib should be reduced to from 140 mg to 280 mg, if a moderate CYP3A inhibitor must be used. Update to contact details for SAE reporting. Update to trial personnel details.

TRIAL SYNOPSIS

Title

IcICLLe: Assessment of the Mechanism of Action of Ibrutinib (PCI-32765) in B-cell Receptor Pathway Inhibition in Chronic Lymphocytic Leukaemia (CLL).

Trial Design

IcICLLe is a feasibility study. All patients will receive continuous oral therapy with ibrutinib (420 mg once daily (OD)) from registration until disease progression. If the patient becomes confirmed minimal residual disease (MRD) negative they will also stop treatment.

The IcICLLe extension study will evaluate the efficacy of ibrutinib plus obinutuzumab in relapse/refractory CLL patients. Relapsed/refractory patients from the IcICLLe study can transfer into this follow-on study.

Objectives

The IcICLLe study (initial phase) will investigate i) the mechanism of action of ibrutinib and ii) the biological response to ibrutinib.

The IcICLLe extension study will investigate; i) the response rate of combined ibrutinib with obinutuzumab on CLL—this will include the proportion of patients who become MRD negative—and, ii) the safety of this novel combination.

Results from the IcICLLe trial will then inform the design of a randomised phase II/III trial using response as the primary outcome measure to determine whether ibrutinib in combination with obinutuzumab, shows sufficient evidence of activity in the cohorts of patients investigated in the IcICLLe trial.

IcICLLe Outcome Measures

Primary outcome measures

Proportion of patients achieving MRD-negative remission by IWCLL criteria (depletion of CLL below 0.01% in the peripheral blood and bone marrow) in a) the initial phase of the study at or before the 6 month assessment, , and b) the Extension Study at or before 9 month assessment. Independent decisions will be made for each study (initial and extension).

Secondary outcome measures:

- Best disease response to treatment: Complete Remission (CR); Complete Remission with incomplete marrow recovery (Cri) or Partial Remission (PR) with leucocytosis, assessed according to the IWCLL Response Criteria (revised 2008) (Appendix 1) in a) the initial phase of the study at or before the 6 month assessment and b) the Extension Study at or before the 9 month assessment. Independent decisions will be made for each study (initial and extension).
- 1 and 2 year progression free survival for relapsed/refractory and treatment naïve patients defined as time from date of registration to date of progression (per the 2008 IWCLL criteria) or death from any cause.
- 1 and 5 year overall survival for relapsed/refractory and treatment naïve patients, defined as the time from date of registration to the date of death from any cause.
- Toxicity of ibrutinib and obinutuzumab
- CLL cell levels as a percentage of total leucocytes in the bone marrow (BM) and absolute counts in the peripheral blood (PB).
- The proportion of patients with >5%, 0.5-5%, <0.5% CLL cells in cell cycle (expressing Ki67) in the peripheral blood and bone marrow in a) the initial phase of the study at or before the 6 month assessment and b) the Extension Study at or before the 9 month assessment.
- Change in the expression levels of CD10, CD103, CD11c, CD185, CD196, CD20, CD200, CD22, CD23, CD25, CD27, CD305, CD31, CD38, CD39, CD43, CD49d, CD5, CD79b, CD81, CD95, IgD,

IgG, or IgM on CLL cells relative to baseline by more than 50% and at least 500 arbitrary units in median fluorescence intensity.

Exploratory outcome measures:

- Change in phosphoprotein expression (including Akt, Syk, MAPK, ERK and Btk) at screening in CLL cells stimulated with immunoglobulin in the presence and absence of *in vitro* ibrutinib and during/after treatment in CLL cells stimulated with immunoglobulin measured as fluorescence intensity in arbitrary units relative to unstimulated cells/control.
- Assessment of the mechanism of response and resistance to ibrutinib and obinutuzumab in patients with lack of or failure to maintain a response or disease progression compared to those patients with good responses (mutation analysis of key BCR pathway genes, gene expression profiling and epigenetic modifications)
- Response correlated with secondary prognostic markers (such as FISH, IGHV, CD38/CD49d expression)
- Change in the expression levels of BCL2, IRF4, ZAP70, CD62L, CD184, CD80, CD40, CD11a, CD54, CD154, CCR7, CD24, CD86 on CLL cells relative to baseline by more than 50% and at least 500 arbitrary units in median fluorescence intensity.
- The absolute numbers and proportions of CD4+ and CD8+ T-cell subsets with respect to expression of CD27, CD62L, CD45RA, CCR4 and CXCR3.
- Assessment of MRD levels using novel technologies including high throughput sequencing

Patient Population

IcICLLe – initial phase – ibrutinib monotherapy

Cohort (A) – treatment naïve CLL patients

Cohort (B) i – relapsed/refractory CLL patients

IcICLLe – Extension Study – ibrutinib and obinutuzumab combination therapy

Cohort (B) ii – ibrutinib naïve relapsed/refractory CLL patients

Cohort (B) iii – patients initially enrolled on the IcICLLe trial in cohort (B)i and treated with at least 6 months of ibrutinib therapy

Sample Size:

IcICLLe

We aim to recruit 20 patients into each cohort: 40 participants in total.

IcICLLe Extension Study

Up to 20 relapsed/refractory patients originally recruited to the IcICLLe study will transition to the extension study (cohort (B) iii). At least 20 relapsed/refractory CLL patients not previously treated in the IcICLLe study (i.e., ibrutinib naïve, cohort (B) ii) will be recruited so that the total sample size in the extension study is no more than 40 patients.

Inclusion and Exclusion Criteria

Inclusion Criteria

Cohort (A): Treatment naïve (initial phase only – 20 patients)

- Progressive Stage A, Stage B or Stage C CLL (Appendix 7)
- CLL requiring therapy by the IWCLL criteria (Appendix 1)
- ECOG performance status (PS) of 0, 1, or 2 (Appendix 6)
- Life expectancy of at least 6 months
- Age ≥18
- Prepared to undergo the stipulated investigations within the trial (including bone marrow examinations)
- Able to give informed consent
- Adequate hepatic function, defined as serum aspartate transaminase (AST) or alanine transaminase (ALT) <2.5 x upper limit of normal (ULN), and total bilirubin ≤1.5 x ULN unless due to Gilbert's syndrome
- Adequate renal function, defined as estimated creatinine clearance ≥30 mL/min using the Cockcroft-Gault equation

Cohorts (B)i and (B)ii: Relapsed/refractory (initial phase 20 patients, extension phase between 20-40 patients)

- B-CLL requiring therapy according to the IWCLL guidelines
    - The leukaemia cells should co-express CD19, CD5, and CD23 and each clone should have restricted to expression of either kappa or lambda immunoglobulin light chains.
    - The levels of surface immunoglobulin, CD20, and CD79b should be low. If there is atypically strong surface immunoglobulin, CD20, or CD79b expression, or other atypical features, it may not be possible to perform the MRD monitoring required to evaluate the primary endpoint.
- Refractory/relapsed CLL defined as any of the following:
    - Failure to achieve a response (CR or PR by IWCLL Criteria) to a purine analogue alone or in combination with chemotherapy, or:
    - Relapse within 6 months of responding to a purine analogue alone or in combination with chemotherapy, or:
    - Relapse at any time after fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine plus rituximab or:
    - Patients with CLL with deletion of chromosome 17p who have failed at least one previous therapy.
- ECOG PS of 0, 1, or 2 (Appendix 6)
- Life expectancy of at least 6 months
- Prepared to undergo the stipulated investigations within the trial (including bone marrow examinations)
- Age ≥ 18
- Able to give informed consent
- Ability to comply with study protocol procedures
- Adequate hepatic function, defined as serum aspartate transaminase (AST) or alanine transaminase (ALT) <2.5 x ULN, and total bilirubin ≤1.5 x ULN unless due to Gilbert's syndrome
- Adequate renal function, defined as estimated creatinine clearance ≥30 mL/min using the Cockcroft-Gault equation
- Minimum platelet count of ≥50 x 10^9/L
- Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L (unless due to direct marrow infiltration by CLL (to be confirmed via bone marrow biopsy)

Cohort (B)iii: Ibrutinib treated patients (extension phase only – up to 20 patients)

- Patients enrolled on IcICLLe trial as relapsed/refractory patients who have received treatment with Ibrutinib on the IcICLLe trial for at least 6 months

Exclusion Criteria

All patients

- Unwilling to undergo the protocol assessments including the bone marrow examinations
- Active infection (at the time of registration)[1], history of chronic or recurrent infection
- Other severe, concurrent (particularly cardiac or pulmonary) diseases or mental disorders that could interfere with their ability to participate in the study
- Use of prior investigational agents within 6 weeks
- Pregnancy or lactation
- Unwilling to use appropriate contraception during and for 18 months following treatment
- Central nervous system (CNS) involvement with CLL
- Mantle cell lymphoma
- Known HIV positive
- Patients with active Hepatitis B disease
  These patients should not be treated. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with ibrutinib in combination with obinutuzumab. At a minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with positive serology for Hepatitis B defined as positivity for Hepatitis B surface antigen (HBsAg) or anti Hepatitis B core antibody (anti-HBc) are excluded from the trial.
- Active secondary malignancy excluding basal cell carcinoma.
- Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification
- Persisting severe pancytopenia (neutrophils <1.0 x10^9/L) or transfusion dependent anaemia unless due to direct marrow infiltration by CLL (to be confirmed via bone marrow biopsy)
- Active haemolysis (not controlled with Prednisolone at 20mg or less)
- Patients requiring or who have received anticoagulation treatment with warfarin or vitamin K antagonists within one week of the first dose of ibrutinib
- Patients requiring concomitant use of strong CYP3A4/5 inhibitors (section 7.8.2)
- Patients with evidence or history of transformation and/or PLL
- Major surgery within 4 weeks prior to registration
- Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to registration History of stroke or intracranial haemorrhage within 6 months prior to registration
- History of severe allergic or anaphylactic reactions to humanised or murine monoclonal antibodies. Known sensitivity or allergy to murine products.
- Vaccination with a live vaccine a minimum of 28 days prior to registration.
- Patients with Progressive Multifocal Leukoencephalopathy (PML).
- No known allergy to obinutuzumab or excipients

Cohort (B)i and (B)ii: Relapsed/refractory (initial phase – 20 patients, extension phase between 20-40 patients)

- Previous treatment with ibrutinib or an alternative inhibitor of B-Cell receptor pathway

Any patients currently participating in IcICLLe and wishing to consent for the IcICLLe extension study will need to meet the relevant eligibility criteria above

[1] Patients may be considered eligible if an active infection is being treated with a short course of antibiotics during the screening period. However, a patient cannot be registered and treated on the trial until the active infection has resolved and the antibiotics have stopped.

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Schedule of Events for IcICLLe

IcICLLe Treatment Schedule (initial phase) (Schedule A)

Assessment		Screening	2 weeks prior to treatment	Day					Month					Every 6 months after 12 months	6 months after clinical complete or MRD negative remission[2]	In the event of disease progression
				1 Pre-treatment	1 (4 hr post 1st dose)	2	8	15	1	3	6	9	12			
Demographic data, medical history, prior diagnosis/treatments		X														
Physical Examination (height, weight, BP, ECOG)		X				X			X	X	X	X	X	X	X	X
Constitutional symptom assessment		X							X		X				X	X
Clinical assessment of liver, spleen and lymph nodes			X			X			X	X	X	X	X	X	X	X
Disease response assessment									X		X				X	X
Local analysis	Haematology and biochemistry	X		X	X	X	X	X	X	X	X	X	X	X	X	X
	Immunology[3]	X		X											X	X
CT Scan		X								X	X[4]				X	
ECG		X							X							
Pregnancy test			X													
Ibrutinib Administration				**Continuous from day 1** (until disease progression or MRD (-)ve remission[2])												
Central analysis (HMDS)	Peripheral Blood		X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Bone Marrow Aspirate		X						X		X				X	X
	Bone Marrow Trephine Biopsy		X						X		X				X	X
Concomitant medication		X		Continuous assessment until 30 days after last administration of Ibrutinib												
Adverse Events				Continuous assessment until 30 days after last administration of Ibrutinib												

[2] See section 7.2.3 for procedure carried out to confirm MRD negative remission, including times points of any additional blood samples and bone marrow examinations, and stopping rules
[3] including serum immunoglobulin & direct antiglobulin
[4] Only if 3 month scan abnormal

cICLLe Extension Study Treatment Schedule (Schedule B)

Assessment		Screening	2 weeks prior to treatment	Day 0		Days 1 -15				Month								Every 6 months after 12 months	6 months after clinical complete or MRD negative remission[5]	In the event of disease progression
				Pre-Ibrutinib treatment	4 hr post Ibrutinib treatment	1	2	8	15	1	2	3	4	5	6	9	12			
Demographic data, medical history, previous treatment		X																		
Physical Examination (height, weight, BP, ECOG, temperature)		X		X		X	X			X		X			X	X	X	X	X	X
Constitutional symptom assessment		X								X					X				X	X
Clinical assessment of liver, spleen and lymph nodes			X	X		X	X			X		X			X	X	X	X	X	X
Disease response assessment										X						X			X	X
Local analysis	Haematology and biochemistry	X		X	X	X[6]	X[5]	X[5]	X[5]	X[5]	(X[5])	X[5]	(X[5])	(X[5])	X	X	X	X	X	X
	Immunology[7]	X			X										X				X	X
Hepatitis B screening		X																		
CT Scan		X										X			X[8]				X	
ECG		X								X										
Pregnancy test			X																	
Ibrutinib administration				**Continuous from day 0**[9] (until disease progression or MRD (-)ve remission[5])																
Obinutuzumab administration						X	X	X	X	X[10]	X[8]	X[8]	X[8]	X[8]						
Central analysis (HMDS)	Peripheral blood		X	X	X	X	X	X	X	X		X			X	X	X	X	X	X
	Bone marrow aspirate and trephine biopsy		X[11]							X[9]						X			X	X
Concomitant medication		X		Continuous assessment until 30 days after last administration of Ibrutinib																
Adverse Events				Continuous assessment until 30 days after last administration of Ibrutinib																

[5] See section 7.2.3 for procedure carried out to confirm MRD negative remission, including time-points of any additional blood samples and bone marrow examinations, and stopping rules

[6] **For patients with creatinine clearance between 30 and 50 mL/min at screening**, **full blood counts and biochemistry must be carried out, before, after and 24 hours after infusion, as described in section 7.1.2**

[7] including serum immunoglobulin & direct antiglobulin (Coombs test)

[8] If 3 month scan abnormal

[9] Ibrutinib naïve patients receive their FIRST dose on day 0 then return to clinic 24 hours later (Day 1) to receive obinutuzumab to help reduce any possible infusion related reactions

[10] Obinutuzumab treatment is on day 1 of cycles 2 to 6 (i.e. at the beginning of each month) – see section 7.1 for details

[11] Exception: patients rolling over from IcICLLe and re-registering within 3 months of bone marrow examination on IcICLLe do NOT need to have further bone marrow examination at screening or 1 month

ABBREVIATIONS

ABPI	ASSOCIATION OF THE BRITISH PHARMACEUTICAL INDUSTRY
AE	ADVERSE EVENT
ALT	ALANINE TRANSAMINASE
ANC	ABSOLUTE NEUTROPHIL COUNT
ASCO	AMERICAN SOCIETY OF CELLULAR ONCOLOGY
AST	ASPARTATE TRANSAMINASE
BCR	B-CELL RECEPTOR
BM	BONE MARROW
BTK	BRUTON'S TYROSINE KINASE
CLL	CHRONIC LYMPHOCYTIC LEUKAEMIA
CNS	CENTRAL NERVOUS SYSTEM
CR	COMPLETE REMISSION
Cri	COMPLETE REMISSION WITH INCOMPLETE MARROW RECOVERY
CRF	CASE REPORT FORM
CR UK	CANCER RESEARCH UK
CRCTU	CANCER RESEARCH UK CLINICAL TRIALS UNIT (UNIVERSITY OF BIRMINGHAM)
CT	COMPUTERISED TOMOGRAPHY
CTCAE	COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS
DCF	DATA CLARIFATION FORM
DSUR	DEVELOPMENT SAFETY UPDATE REPORT
ECG	ELECTROCARDIOGRAMS
ECOG	EASTERN COOPERATIVE ONCOLOGY GROUP
FBC	FULL BLOOD COUNT
FCR	FLUDARABINE, CYCLOPHOSPHAMIDE AND RITUXIMAB
GCP	GOOD CLINICAL PRACTICE
GDPR	GENERAL DATA PROTECTION REGULATION
GP	GENERAL PRACTITIONER
HIV	HUMAN IMMUNODEFICIENCY VIRUS
HMDS	HAEMATOLOGICAL MALIGNANCY DIAGNOSTIC SERVICE
IB	INVESTIGATOR BROCHURE
ICF	INFORMED CONSENT FORM
IMP	INVESTIGATIONAL MEDICINAL PRODUCT
IR	IONIZING RADIATION
IRR	INFUSION RELATED REACTION
ISF	INVESTIGATOR SITE FILE
IWCLL	INTERNATIONAL WORKSHOP ON CHRONIC LYMPHOCYTIC LEUKAEMIA
LDT	LYMPHOCYTE DOUBLING TIME
MCL	MANTLE CELL LYMPHOMA
MDS	MYELODYSPLASTIC SYNDROME
MHRA	MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY
MRD	MINIMAL RESIDUAL DISEASE
MRI	MAGNETIC RESONANCE IMAGING
OD	ONCE DAILY
ORR	OVERALL RESPONSE RATE

OS	OVERALL SURVIVAL
PB	PERIPHERAL BLOOD
PFS	PROGRESSION FREE SURVIVAL
PI	PRINCIPAL INVESTIGATOR
PIS	PATIENT INFORMATION SHEET
PK	PHARMACOKINETICS
PR	PARTIAL REMISSION
RNA	RIBOSE NUCLEIC ACID
TLS	TUMOUR LYSIS SYNDROME
TNO	TRIAL NUMBER
T-PLL	T-PROLYMPHOCYTIC LEUKAEMIA
SAE	SERIOUS ADVERSE EVENT
SAR	SERIOUS ADVERSE REACTION
SD	STABLE DISEASE
SUSAR	SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION
TMG	TRIAL MANAGEMENT GROUP
ULN	UPPER LIMIT OF NORMAL
WBC	WHITE BLOOD COUNT
WHO	WORLD HEALTH ORGANIZATION
WMA	WORLD MEDICAL ASSEMBLY

Table of contents

1. BACKGROUND AND RATIONALE

1.1 Background

Chronic lymphocytic leukaemia (CLL) is the most common haematological malignancy in the western world with an incidence of 6.5 per 100,000 per year which increases with age so that the incidence is over 30 per 100,000 per year in individuals over 75 years old (1). As the population ages, CLL will therefore become a greater problem for individuals and society. CLL is also notable because of its extreme clinical variability. Some patients never require therapy and have a normal lifespan however in others, disease progression leads to chronic illness, poor quality of life and reduced survival.

The clinical manifestations of CLL occur because of the accumulation of malignant B cells, which leads to progressive immune dysfunction and tissue infiltration. The former results in an increased susceptibility to infection and a propensity to autoimmune cytopenia, whilst the later gives rise to enlargement of the lymph nodes, liver, spleen and other organs. Infiltration of the bone marrow eventually causes haematopoietic failure, which compounds the susceptibility to infection. Some patients with very indolent disease experience few, if any, problems and never require therapy having a survival no different from age-matched controls (2). However in many patients the disease pursues a more aggressive course with a significant burden of ill health and reduced life expectancy, estimated for the whole CLL population at 10 years from diagnosis.

Although CLL cells in the blood are largely non-dividing, it is now realised that extensive cell division occurs in proliferation centres or pseudofollicles in secondary lymphoid tissues, such as the lymph nodes and spleen, with up to 1-2% of the total tumour renewed each day (3). This proliferation appears to depend on signalling through the B-cell receptor (BCR).

Current treatments which depend on cytotoxic chemotherapy with or without monoclonal antibodies, such as rituximab, are relatively effective leading to remissions in the majority of patients. However these therapies are not curative with patients inevitably relapsing and are associated with toxicity leading to significant immediate and late complications. The recent advances in the understanding of the pathophysiology of CLL with proliferation apparently dependent on signalling through the BCR provide a rationale for targeting downstream signalling from the BCR as a novel treatment approach in CLL. The hope of such targeted therapy is to improve the duration of responses without the non-specific toxicity observed with current treatment approaches.

1.2 Trial Rationale

1.2.1 Justification for patient population

The prevalence of CLL increases with advancing age, so that more than 50% of patients are older than 70, thus limiting the applicability of intensive and potentially curative therapies such as allogeneic bone marrow transplantation and chemotherapy combinations. Since CLL is presently incurable using all other drug or antibody based interventions, the development of non-toxic modes of treatment that prevent or delay the progression of early stage CLL is thus a highly desirable goal and forms the rationale for the proposed study.

1.2.2 IcICLLe Justification for design

For relapse/refractory patients a treatment with a low toxicity may be of particular importance as a replacement for the current highly toxic and intensive therapies. The safety and efficacy of ibrutinib has been evaluated in a number of other studies and clearly this class of drugs promises to represent a major step forward in our treatment of CLL. However there has been no detailed investigation of its mechanism of action. By studying the mechanism of action of ibrutinib we hope to ascertain the most logical agents to use in combination with ibrutinib and how these agents should be combined in order to complement their modes of action and thus their effectiveness. It is critically important to perform these studies now so that our planned Phase II and III trials are optimally designed.

1.2.3 IcICLLe extension study Justification for design

The IcICLLe extension study will test the safety and efficacy of ibrutinib combined with obinutuzumab in CLL. A major aim of treatment in CLL is to eradicate detectable minimal residual disease (MRD). Ibrutinib is a major step forward in the treatment of CLL but results in an immediate lymphocytosis that persists in most patients for at least several months. However the combination of ibrutinib with rituximab, a relatively ineffective monotherapy in CLL, seems to abrogate the lymphocytosis. Obinutuzumab is a second generation anti-CD20 monoclonal antibody which appears to be highly effective in CLL resulting

in a rapid eradication of peripheral blood lymphocytosis and the eradication of MRD in a proportion of patients. Currently we only have data in untreated CLL for obinutuzumab vs. Rituximab. Therefore the combination of obinutuzumab with ibrutinib is likely to be extremely effective. It may also inform possible future Phase III trials to test a more effective anti-CD20 antibody in combination with ibrutinib.

1.3 Ibrutinib

Ibrutinib (PCI-32765) is a specific and irreversible inhibitor of Bruton's Tyrosine Kinase (BTK) that has been developed by Pharmacyclics LLC (now in partnership with Johnson & Johnson). BTK is an essential part of the BCR signalling pathway which is required for tumour expansion and proliferation. Ibrutinib blocks this signalling and induces apoptosis as well as inhibiting CLL cell migration and adhesion (4). However the exact nature of this pathway downstream from BTK is still unknown.

Recent Phase I/II trials of inhibitors of intra-cellular signalling from the BCR in patients with heavily pre-treated and refractory CLL have demonstrated extremely promising activity (5). In all patients who remain on treatment for over 4 weeks there is evidence of clinical activity with a reduction in lymph node size. The improvement in lymphadenopathy is seen within the first 4 to 8 weeks of therapy but during this time there is also an increase in lymphocytosis. With continued ibrutinib treatment the lymph nodes continue to respond and the lymphocytosis improves over a period typically around 6 months. We hypothesise that the activity of ibrutinib is by inhibiting signalling through the BCR and thereby stopping the proliferation of the CLL cells in the tissue compartment and interfering with the cycling of CLL cells. This most likely initially leads to the redistribution of CLL cells from the tissue compartment into the peripheral blood, hence the early lymphocytosis observed during therapy. We would then hypothesise that this leads to a reduction in the proliferating compartment with presumably the disruption of the proliferation centres in the tissue compartment and the subsequently a reduction in the production of CLL cells leading to the impressive responses that have been observed.

Results from previous phase I studies of this drug have found an oral dose of 420 mg once a day (OD) to be active with 24h target inhibition (4). Results from these early studies indicated that the drug has a reduced toxicity profile compared to standard CLL therapy with high response rates. The results from this trial will be used to inform the design of a randomised phase II/III trial of either ibrutinib alone or in combination with other drugs, such as CD20 antibodies compared to the current standard treatment.

The pre-clinical experience, toxicology and pharmacology and clinical experience are fully described in the current version of the Investigators Brochure (IB).

1.3.1 Safety of ibrutinib in clinical trials

Summary of Clinical Data:Monotherapy Studies

Pooled safety data for subjects treated with ibrutinib monotherapy in 13 studies that have completed primary analysis as of 31 May 2016 cutoff date for the current IB update in B-cell malignancies are summarized below.

The most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N =1318)

Most frequently reported TEAEs ≥ 15% [a]	Most frequently reported Grade 3 or 4 TEAEs ≥ 3% [b]	Most frequently reported Serious TEAEs ≥ 2% [c]
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Pyrexia	Hypertension	
Anemia	Diarrhea	
Neutropenia	Atrial fibrillation	
Upper respiratory tract infection		
Thrombocytopenia		
Oedema peripheral		

[a] Source is Table 6 of IB (v10), [b] Source is Table 8 of IB (v10), [c] Source is Table 9 of IB (v10).

Combination Therapy Studies

Pooled safety data from a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies conducted in subjects with B-cell malignancies, are briefly summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

The most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N = 423):

Most frequently reported TEAEs ≥ 20% [a]	Most frequently reported Grade 3 or 4 TEAEs ≥ 3% [b]	Most frequently reported Serious TEAEs ≥ 2% [c]
Neutropenia	Neutropenia	Pneumonia
Diarrhea	Thrombocytopenia	Febrile neutropenia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Neutrophil count decreased	Cellulitis
Anemia	Anemia	
Pyrexia	Fatigue	
	Hypertension	
	Diarrhea	

[a] Source is Table 10 of IB (v10), [b] Source is Table 12 of IB (v10), [c] Source is Table 13 of IB (v10).

1.4 Obinutuzumab

Obinutuzumab is a novel glycoengineered monoclonal antibody targeting the CD20 antigen, by selectively binding to the extracellular domain of the human CD20 antigen on malignant human B cells. Obinutuzumab has the following characteristics:[5]

- High-affinity binding to CD20
- Compared with the chimeric Type I anti-CD20 antibody rituximab, increased antibody-dependent cell-mediated cytotoxicity (ADCC, due to glycoengineering) related to an improved binding of obinutuzumab to the different allotypes of Fc-RIIIa expressed by natural killer (NK) cells and monocytes
- Compared with rituximab, increased direct cell death induction related to an elbow hinge amino exchange of the Fab region and Type II binding of the CD20 epitope
- Type II binding to the CD20 epitope, leading to low complement-dependent cytotoxicity (CDC) related to the recognition of the CD20 epitope and the lack of CD20 localization into lipid rafts after binding of the monoclonal antibody to CD20

Obinutuzumab follows a two-compartment model comprising a time-varying clearance pathway and a linear clearance pathway provides an adequate description of the pharmacokinetics of obinutuzumab following IV administration. Following the infusion of obinutuzumab, the elimination appears to be characterised by a linear clearance pathway that is dependent on time (i.e., starting at a typical value of 630 mL/day and then gradually decreasing to an asymptote of 60 mL/day at steady state). Tumour burden may potentially contribute significantly to the clearance of obinutuzumab, especially at the beginning of treatment when CD20-positive tumour cells are most abundant. As tumour burden decreases, the clearance reaches an asymptote, which is believed to be primarily a function of the proteolytic metabolic clearance. Therefore, the use of obinutuzumab as consolidation therapy when the tumour bulk is at a minimum should increase the levels of bioavailable drug. Treatment with obinutuzumab results in extensive B-cell depletion, with all patients showing a reduction in B-cell counts

to absolute zero at some stage of their treatment cycle. Overall, there has been no notable increase in complement levels before and after infusion, but transient changes have been observed in the levels of interleukin (IL)-6 and IL-8 before and after infusion.

Obinutuzumab appears to have greater efficacy in treatment naïve CLL when in combination with chlorambucil vs. rituximab with reports of MRD negativity when used to treat progressive CLL. In addition, as the cells targeted by obinutuzumab are B-cells, rather than all lymphocytes, including T-cells. The study of obinutuzumab within the clinical trial setting has demonstrated a rapid response in peripheral blood lymphocytosis, with early reports of patients achieving MRD negativity with obinutuzumab.[7-9]

1.4.1 Safety of obinutuzumab in clinical trials

Up to 2 July 2015, data from an estimated 1281 patients with CLL and 2105 NHL patients are available for safety analysis of obinutuzumab in clinical trials (reference: Investigator's Brochure V 10, date 10-Sep-2015). Patients across the 15 studies received doses of 50 mg to 2000 mg in monotherapy or in combination with CHOP, FC, bendamustine, or chlorambucil. Studies BO20999, BO21003, YP25623 and JO21900 are now closed. The primary analyses for studies BO21000, BO21004, GAO4779g, GAO4768g, GAO4915g, GAO4753g, have been performed but data is still being collected. Studies BO21223, BO21005, BO29448, JO29737, and MO28543 are on-going and the primary analyses have not been performed. The safety data presented from the Phase III studies MO28543, BO21005 and BO21223 are blinded.

Up to 2 July 2014, the following AEs are considered as important risks associated or potentially associated with obinutuzumab: IRRs, TLS, thrombocytopenia including acute thrombocytopenia, neutropenia, prolonged B-cell depletion, infections including PML and HBV reactivation, worsening of pre-existing cardiac conditions, impaired immunisation response, immunogenicity, and second malignancies.

Monotherapy Studies

A pooled analysis of studies BO20999 and BO21003 Phase I/II was conducted, including 205 patients with NHL (49 aNHL and 156 iNHL patients) and 38 patients with CLL who received obinutuzumab.

Thirteen (34%) CLL and 61 (30%) NHL patients experienced fatal events. The most frequent causes of death were disease progression (N=52) followed by pneumonia (N=2).

Seventeen (45%) CLL and 57 (28%) NHL patients experienced at least one SAE. The most frequent SAEs experienced by CLL patients were IRRs (16%), febrile neutropenia (11%), and pyrexia (5%). The most frequent SAEs experienced by NHL patients were IRRs (3%), febrile neutropenia (2%) and pneumonia (2%).

Thirty (79%) CLL and 85 (42%) NHL patients experienced Grade 3 or 4 AEs. In CLL patients, the most frequent Grade 3 or 4 AEs were IRRs (29%) and neutropenia (34%). In NHL patients, the most frequent Grade 3 or 4 AEs were IRRs (9%) followed by neutropenia (7%) and lymphopenia (6%). Four (11%) patients with CLL and 11 (5%) patients with NHL experienced AEs leading to withdrawal of obinutuzumab. The most frequent AE leading to obinutuzumab withdrawal among patients with NHL was IRRs (2%) and hypotension (2%).

Combination Therapy Studies

The largest and most meaningful dataset to assess the safety of obinutuzumab in combination (with chlorambucil) therapy in patients with CLL comes from study BO21004/CLL11.

Fatal AEs occurred in 5.7% and 7.5% of patients in the GClb and RClb arms, respectively. The incidence of SAEs in the GClb and RClb arms was 42.0% and 36.8% respectively, the incidence of Grade 3-4 AEs was 70.5% and 56.7% respectively, and the incidence of AEs leading to withdrawal of any study medication was 20.2% and 15.3%, respectively.

Imbalances between the treatment arms in AEs, SAEs and Grade 3-5 AEs was mainly due to IRRs, which occurred primarily during the first infusion of obinutuzumab. IRRs were experienced by 238/336 patients (70.8%) who received GClb and led to the treatment withdrawal of 27/336 patients (11.3%).

Infusion Related Reactions

In both monotherapy and combination therapy studies the most frequently observed adverse events in patients receiving obinutuzumab were infusion-related reactions (IRR). ; These occurred predominantly during infusion of the first 1000 mg. The incidence and severity of infusion related symptoms decreased substantially with subsequent infusions, with most patients having no IRRs during the second and subsequent administrations of obinutuzumab. Patients with a high tumour burden (i.e. high peripheral lymphocyte count in CLL (> 25 x 10^9/L) may be at increased risk of severe IRR. The commonly experienced IRRs are characterised by hypotension, fever, chills, flushing, nausea, vomiting, hypertension, and fatigue, among other symptoms. In the majority of patients, IRRs were mild or moderate and could be managed. Hypersensitivity may be difficult to distinguish from infusion related reactions; anaphylaxis has been reported in patients treated with obinutuzumab.

2. AIMS, OBJECTIVES AND OUTCOME MEASURES

2.1 Aims and Objectives

The aim of this study is to investigate the mechanism of action of ibrutinib. Results from this trial will then inform the IcICLLe extension study using MRD negative response as the primary outcome measure to determine whether ibrutinib and ibrutinib in combination with obinutuzumab shows sufficient evidence of activity in these cohorts of patients. The combination of obinutuzumab and ibrutinib is currently under investigation in a phase III trial.

2.2 Outcome Measures

Primary outcome measures

Proportion of patients achieving MRD-negative remission by IWCLL criteria (depletion of CLL below 0.01% in the peripheral blood and bone marrow) in a) the initial phase of the study at or before the 6 month assessment and b) the Extension Study at or before the 9 month assessment. Independent decisions will be made for each study (initial and extension).

Secondary outcome measures:

- Best disease response to treatment: Complete Remission (CR); Complete Remission with incomplete marrow recovery (Cri) or Partial Remission (PR) with leucocytosis, assessed according to the IWCLL Response Criteria (revised 2008) (Appendix 1) in a) the initial phase of the study at or before the 6 month assessment and b) the Extension Study at or before the 9 month assessment. Independent decisions will be made for each study (initial and extension 1 and 2 year progression free survival for relapsed/refractory and treatment naïve patients defined as time from date of registration to date of progression (per the 2008 IWCLL criteria) or death from any cause
- 1 and 5 year overall survival for relapsed/refractory and treatment naïve patients, defined as the time from date of registration to the date of death from any cause
- Toxicity of ibrutinib and obinutuzumab
- CLL cell levels as a percentage of total leucocytes in the bone marrow (BM) and absolute counts in the peripheral blood (PB)
- The proportion of patients with >5%, 0.5-5%, <0.5% CLL cells in cell cycle (expressing Ki67) in the peripheral blood and bone marrow in a) the initial phase of the study at or before the 6 month assessment and b) the Extension Study at or before the 9 month assessment
- Change in the expression levels of CD10, CD103, CD11c, CD185, CD196, CD20, CD200, CD22, CD23, CD25, CD27, CD305, CD31, CD38, CD39, CD43, CD49d, CD5, CD79b, CD81, CD95, IgD, IgG, or IgM on CLL cells relative to baseline by more than 50% and at least 500 arbitrary units in median fluorescence intensity

Exploratory outcome measures:

- Change in phosphoprotein expression (including Akt, Syk, MAPK, ERK and Btk) at screening in CLL cells stimulated with immunoglobulin in the presence and absence of *in vitro* ibrutinib and during/after treatment in CLL cells stimulated with immunoglobulin measured as fluorescence intensity in arbitrary units relative to unstimulated cells/control
- Assessment of the mechanism of response and resistance to Ibrutinib and obinutuzumab in patients with lack of or failure to maintain a response or disease progression compared to those patients

with good responses (mutation analysis of key BCR pathway genes, gene expression profiling and epigenetic modifications)

- Response correlated with secondary prognostic markers (such as FISH, IGHV, CD38/CD49d expression)
- Change in the expression levels of BCL2, IRF4, ZAP70, CD62L, CD184, CD80, CD40, CD11a, CD54, CD154, CCR7, CD24, CD86 on CLL cells relative to baseline by more than 50% and at least 500 arbitrary units in median fluorescence intensity
- The absolute numbers and proportions of CD4+ and CD8+ T-cell subsets with respect to expression of CD27, CD62L, CD45RA, CCR4 and CXCR3
- Assessment of MRD levels using novel technologies including high throughput sequencing

3. ICICLLE TRIAL DESIGN

IcICLLe Study (initial phase)

A feasibility study to investigate i) the mechanism of action of ibrutinib and ii) the biological response to ibrutinib in two separate cohorts of patients; (A) treatment naïve and (B)i relapsed/refractory CLL.

There will be 20 patients in each cohort; therefore a total of 40 patients will initially be recruited.. All patients will receive continuous oral therapy with ibrutinib (420 mg OD) from registration until disease progression.

We will test the patterns of response to ibrutinib in both the treatment naïve and the relapsed/refractory patient cohorts.

IcICLLe Extension Study

The *IcICLLe extension study* will investigate if ibrutinib combined with obinutuzumab can increase the number of patients achieving MRD negativity in peripheral blood and bone marrow.

Two cohorts of patients will be evaluated; cohort (B)ii ibrutinib naïve relapsed/refractory CLL patients, and cohort (B)iii patients initially enrolled on the IcICLLe trial as relapsed/refractory patients and treated with at least 6 months of ibrutinib therapy (i.e. previously in cohort (B)i).

Please note that treatment naïve patients enrolled on IcICLLe in the initial phase—cohort (A)—will not be eligible to take part in the IcICLLe Extension Study and thus will continue with ibrutinib monotherapy.

In the IcICLLe extension study, ibrutinib and obinutuzumab will be administered in combination. Ibrutinib will be given as continuous oral therapy (420 mg OD) from registration until disease progression. **The ibrutinib naive cohort in the IcICLLe extension study should receive ibrutinib 24 hours before the obinutuzumab (Day 0) to help reduce potential infusion reactions.** Obinutuzumab will be given intravenously at a dose of 1000 mg on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2- 6 (see section 7.1 for further information of obinutuzumab scheduling)

We will test the patterns of response to ibrutinib and obinutuzumab in both the ibrutinib-naïve and ibrutinib-treated relapsed/refractory patient cohorts.

By studying this and deriving the mechanism of action in both treatment arms we hope to ascertain the most appropriate drugs to combine with ibrutinib and inform how this might be done. This will help to define if this is an appropriate drug to use in combination and/or to take forward into randomised Phase II/III trials of ibrutinib in CLL.

Participants will be recruited from TAP centres with expertise in the diagnosis and treatment of CLL. It is envisaged that all eligible patients at these centres will be offered the opportunity to participate in the study.

Assessment of response

Assessment of MRD will be carried out on peripheral blood samples throughout the study. It will be measured by flow and assessed using current IWCLL guidelines (refer to Appendix 1 for these guidelines and references). Assessment of MRD in bone marrow will be carried out on monotherapy patients after 6 months of continuous treatment with ibrutinib, and for combination therapy patients at 9 months (3 months after completion of combination therapy to allow for washout of antibodies). This is in line with comparable studies and IWCLL guidelines on assessment of MRD; that is to say that response should be assessed 2 months after the treatment has finished. Whilst extension study patients will continue on ibrutinib monotherapy after the 6 cycles of obinutuzumab, the effect of any synergy between ibrutinib and obinutuzumab should be evaluated after cessation of the second IMP. We can thus determine if administration of the combination therapy leads to a sustained response in patients when examining MRD in both peripheral blood at 1, 3, 6 and 9 months and bone marrow at 1 and 9 months.

Biological response will be assessed by way of peripheral blood and/or bone marrow examinations taken over a 12 month period. Further samples will also be collected every 6 months after this date, and 6 months after the patients achieve a clinical complete or MRD negative remission. If patients become confirmed MRD negative they will also stop treatment.

The key biological end-points will be complete following 6 months of trial treatment with secondary end-points of Modified IWCLL Response Criteria continuing to 12 months and beyond if patients continue to respond.

3.1 Translational Studies

The studies described below are optional translational studies.

3.1.1 Kinetics Sub Study (Appendix 8):

This sub-study will be run alongside the IcICLLe trial at a limited number of centres.

If your centre is running the Kinetics Sub Study, patients should be given the option to participate in a 'Kinetics Study', which will run alongside IcICLLe and will be based at King's College Hospital London. An assessment of tumour proliferation rate will be assessed using flow sorted CLL cells and will measure proliferation by the in-vivo incorporation of deuterated glucose (^{2}D-Glc) into the leukemic cells.

3.1.2 Biobanking of samples with the UK CLL Trials Biobank (Appendix 9):

Patients taking part in the IcICLLe trial may also be approached to donate samples to the UK CLL Trials Biobank. This is separate research involving

4. ELIGIBILITY

4.1 Inclusion Criteria

Cohort (A): Treatment naïve (initial phase only – 20 patients)

- Progressive Stage A, Stage B or Stage C CLL (Appendix 7)
- CLL requiring therapy by the IWCLL criteria (Appendix 1)
- ECOG performance status (PS) of 0, 1, or 2 (Appendix 6)
- Life expectancy of at least 6 months
- Age ≥18
- Prepared to undergo the stipulated investigations within the trial (including bone marrow examinations)
- Able to give informed consent
- Adequate hepatic function, defined as serum aspartate transaminase (AST) or alanine transaminase (ALT) <2.5 x ULN, and total bilirubin ≤1.5 x ULN unless due to Gilbert's syndrome
- Adequate renal function, defined as estimated creatinine clearance ≥ 30 ml/min using the Cockcroft-Gault equation

Cohort (B)i and (B)ii: Relapsed/refractory (initial phase – 20 patients, extension phase between 20-40 patients)

- B-CLL requiring therapy according to the IWCLL guidelines
    - The leukaemia cells should co-express CD19, CD5, and CD23 and each clone should have restricted to expression of either kappa or lambda immunoglobulin light chains.
    - The levels of surface immunoglobulin, CD20, and CD79b should be low. If there is atypically strong surface immunoglobulin, CD20, or CD79b expression, or other atypical features, it may not be possible to perform the MRD monitoring required to evaluate the primary endpoint.[12]
- Refractory/relapsed CLL defined as any of the following:
    - Failure to achieve a response (CR or PR by IWCLL Criteria) to a purine analogue alone or in combination with chemotherapy, or:
    - Relapse within 6 months of responding to a purine analogue alone or in combination with chemotherapy, or:
    - Relapse at any time after fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine plus rituximab, or:
    - Patients with CLL with deletion of chromosome 17p who have failed at least one previous therapy.
- ECOG PS of 0, 1, or 2 (see Appendix 6)
- Life expectancy of at least 6 months
- Prepared to undergo the stipulated investigations within the trial (including bone marrow examinations)
- Age ≥ 18
- Able to give informed consent
- Ability to comply with study protocol procedures
- Adequate hepatic function, defined as serum aspartate transaminase (AST) or alanine transaminase (ALT) <2.5 x ULN, and total bilirubin ≤1.5 x ULN unless due to Gilbert's syndrome
- Adequate renal function, defined as estimated creatinine clearance ≥30 mL/min using the Cockcroft-Gault equation
- Minimum platelet count of ≥50 x 10^9/L
- Absolute neutrophil count ≥ 1.0 x 10^9/L (unless due to direct marrow infiltration by CLL (to be confirmed via bone marrow biopsy)

Cohort (B)iii: Ibrutinib treated patients (extension phase only – up to 20 patients)

Patients enrolled on the IcICLLe trial as relapsed/refractory patients who have received treatment with Ibrutinib on the IcICLLe trial for at least 6 months

[12] If there are known to be any atypical features, please send a peripheral blood to HMDS for evaluation at least two weeks prior to the screening bone marrow sample.

4.2 Exclusion Criteria

All patients

- Unwilling to undergo the protocol assessments including the bone marrow examinations
- Active infection (at the time of registration) [13], history of chronic or recurrent infection
- Other severe, concurrent (particularly cardiac or pulmonary) diseases or mental disorders that could interfere with their ability to participate in the study
- Use of prior investigational agents within 6 weeks
- Pregnancy or lactation
- Unwilling to use appropriate contraception during and for 18 months following treatment
- Central nervous system (CNS) involvement with CLL
- Mantle cell lymphoma
- Known HIV positive
- Patients with active Hepatitis B disease
  These patients should not be treated. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with [Ibrutinib in combination with obinutuzumab]. At a minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with positive serology for Hepatitis B defined as positivity for Hepatitis B surface antigen (HBsAg) or anti Hepatitis B core antibody (anti-HBc) are excluded from the trial
- Active secondary malignancy excluding basal cell carcinoma
- Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification
- Persisting severe pancytopenia (neutrophils <1.0 x10^9/L) or transfusion dependent anaemia unless due to direct marrow infiltration by CLL (to be confirmed via bone marrow biopsy)
- Active haemolysis (not controlled with Prednisolone at 20 mg or less)
- Patients requiring or who have received anticoagulation treatment with warfarin or vitamin K antagonists within one week of the first dose of ibrutinib
- Patients requiring concomitant use of strong CYP3A4/5 inhibitors (section 7.8.2)
- Patients with evidence or history of transformation and/or PLL
- Major surgery within 4 weeks prior to registration
- Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to registration
- History of stroke or intracranial haemorrhage within 6 months prior to registration
- History of severe allergic or anaphylactic reactions to humanised or murine monoclonal antibodies. Known sensitivity or allergy to murine products.
- Vaccination with a live vaccine a minimum of 28 days prior to registration.
- Patients with Progressive Multifocal Leukoencephalopathy (PML).
- No known allergy to obinutuzumab or excipients

Cohort (B)i and(B)ii: Relapsed/refractory (initial phase – 20 patients, extension phase 20-40 patients)

- Previous treatment with ibrutinib or an alternative inhibitor of B-Cell receptor pathway

In terms of exclusion criteria; patients currently participating in IcICLLe and wishing to consent for the IcICLLe extension study must not contravene any of the exclusion criteria <u>above.</u>

Please note that treatment naïve patients enrolled on IcICLLe will not be eligible to take part in the IcICLLe Extension Study.

[13] Patients may be considered eligible if an active infection is being treated with a short course of antibiotics during the screening period. However, a patient cannot be registered and treated on the trial until the active infection has resolved and the antibiotics have stopped.

5. SCREENING AND CONSENT

5.1 Informed Consent

It is the responsibility of the Investigator or delegate, to obtain written informed consent for each patient prior to performing any trial related procedure. A Patient Information Sheet is provided to facilitate this process. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the patient. The Investigator should also stress that the patient is completely free to refuse to take part or withdraw from the trial at any time. The patient should be given ample time (e.g. 24 hours) to read the Patient Information Sheet and to discuss their participation with others outside of the site research team. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

If the patient expresses an interest in participating in the trial they should be asked to sign and date the latest version of the Informed Consent Form. The Investigator or designate must then sign and date the form. A copy of the Informed Consent Form should be given to the patient, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Once the patient is entered into the trial the patient's trial number should be entered on the Informed Consent Form maintained in the ISF. In addition, if the patient has given explicit consent a copy of the signed Informed Consent Form must be sent in the post to the Trials Office for review.

Details of the informed consent discussions should be recorded in the patient's medical notes, this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the Patient Information Sheet and Informed Consent Form. Throughout the trial the patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient in which case the process above should be followed and the patient's right to withdraw from the trial respected. The patient should be given ample time to read changes made to the patient information sheet, and may re-consent at the same visit that new information is provided, if they wish to do so.

Electronic copies of the Patient Information Sheet and Informed Consent Form are available from the Trials Office and should be printed or photocopied onto the headed paper of the local institution.

Details of all patients approached about the trial should be recorded on the Patient Screening/Enrolment Log and with the patient's prior consent their General Practitioner (GP) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose.

Translational Studies

Before proceeding with and/or collecting samples for either of the translational-studies, the informed consent procedure must be followed as directed for each translational-study.

5.2 Extension study

Patients enrolled as relapsed/refractory patients and treated with ibrutinib on the IcICLLe trial will be given the opportunity to join the IcICLLe extension study. Those who wish to join will be required to consent for this study via the IcICLLe extension study Patient Information sheet and consent form.

Patients who do not wish to enrol onto the extension study or those who are not eligible for it should continue to receive ibrutinib monotherapy and be followed up in accordance with Schedule A. Any additional safety information or changes relevant to the patients continuing on ibrutinib monotherapy will be given to patients in an addendum patient information sheet in order for them to re-consent and continue on study if they wish to do so.

5.3 Screening / Baseline

Following informed consent, the following samples will be provided for screening/baseline purposes:

5.3.1 Assessments 4 weeks prior to treatment start date

These assessments are to be performed **within the four weeks** prior to registration and following consent unless conducted as part of standard clinical practice.

Complete medical history: Detailed history of CLL, baseline clinical conditions

Complete physical examination:

- Blood pressure
- Pulse
- Temperature
- Height
- Weight
- ECOG performance status

Local laboratory tests:

Haematology:

- Haemoglobin
- Lymphocyte count
- Neutrophil count
- Platelet count
- Reticulocyte count
- White blood cell count (with differential count)

Biochemistry

- Albumin
- Alkaline Phosphatase (ALP)
- ALT or AST
- Calcium (adjusted)
- Creatinine
- eGFR
- Glucose
- LDH
- Phosphate
- Potassium
- Sodium
- Total Bilirubin
- Total Protein
- Urea
- Urate

Immunology:

- Direct coombs test
- Serum immunoglobulins and electrophoresis
- β_2 microglobulin concentration

Hepatitis B screening

- Minimum: HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines.
- HBV DNA PCR should be performed to if HBcAb is likely due to cross reactivity with IVIg. If this is negative the patient is eligible for screening. . Following the last dose of obinutuzumab, these patients should undergo HBV DNA PCR at all study visits for two years.

CT-scan: thorax, abdomen and pelvis to assess lymph node disease[14]

CT scans will be performed locally at IcICLLe trial sites. Reports may be requested for central review by members of the TMG. Redacted reports (where the patient is identified only by TNO) will be requested by email.

ECG: should be performed to assess patient for signs of atrial fibrillation

Constitutional symptom assessment: Assessments of fatigue, unintentional weight loss, fevers and night sweats.

Concomitant medication: Details should be recorded from 4 weeks before start of treatment.

[14] If the patient has had a CT scan within 8 weeks of the proposed treatment start date this may be used as part of the screening process in order to reduce patient exposure to ionising radiation.

If there is any doubt regarding the immunological phenotype of the patients disease please send a peripheral blood sample to HMDS for evaluation at least two weeks prior to the screening bone marrow sample

5.3.2 Assessments 2 weeks before the treatment start date

These assessments are to be performed **within the two weeks** prior to registration and following consent

- **Clinical assessment of lymph node disease**:
  - The size of the largest lymph nodes in each nodal area (cervical, axillary and inguinal) should be measured in centimetres in 2-dimensions
- **Clinical assessment of liver and spleen**:
  - If palpable, size of liver and spleen below costal margin should be measured.
- **Pregnancy test** (in women of child bearing potential **within 2 weeks** prior to starting treatment)
- **Samples to send for central analysis** (see section 7.3 for details of how to do this):
  - 0.5 - 2 mL first-pull bone marrow aspirate

    The first draw of bone marrow aspirate should be put in EDTA and is used for MRD flow cytometry (the less the marrow is diluted with blood the more accurate the assessment of involvement by CLL).
  - Bone marrow trephine biopsy (directly in formalin)
  - 4 x 5 mL peripheral blood in EDTA

Please note:

1. Samples sent for central analysis must be sent on Monday or Tuesday two weeks prior to the provisional treatment start date agreed with the IcICLLe trial office.
2. Confirmation by the HMDS that this two week peripheral blood sample is viable will be required before the patient starts treatment. If this sample is not viable, an additional peripheral blood sample will be requested and confirmed to be viable before the patient starts ibrutinib treatment.
3. IcICLLe Extension Study patients who are rolling over from IcICLLe and have undergone bone marrow examination within 6 months of starting the Extension Study are NOT required to have bone marrow examinations at screening

6. TRIAL ENTRY

Patients must be registered with the Cancer Research UK Clinical Trials Unit (CRCTU) at the University of Birmingham. The patient's eligibility will be confirmed at registration. If eligible for the study, the patient will be allocated a Patient Trial Number (TNO). The registration line will be open during office hours (9-5pm, Monday-Friday).

Registration line: 0121 371 7864
Monday - Friday, 9-5pm

IcICLLe Extension Study

Relapsed/refractory patients who have received ibrutinib on IcICLLe who wish to join the extension study need to consent and (re-)register for the extension study. Ibrutinib naïve patients will need to consent and be registered for the IcICLLe extension study. **All patients entering the extension study will receive a new trial number (TNO).**

7. TREATMENT DETAILS

7.1 Trial Treatment

Ibrutinib and obinutuzumab are both Investigational Medicinal Products (IMPs) in this study.

All patients will receive continuous oral therapy with ibrutinib (420 mg OD) from registration until disease progression (as per the modified IWCLL response criteria (revised 2008) in appendix 2).

Patients in the IcICLLe extension study will additionally receive obinutuzumab intravenously for up to 6 cycles of therapy. This will be given at a dose of 1000 mg on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2-6 (see schedule A and B). If the patient becomes confirmed MRD negative they will also stop ibrutinib/obinutuzumab treatment (see section 7.2.3).

Please see Section 7.6 for supportive treatments for ibrutinib and obinutuzumab.

7.1.1 Ibrutinib treatment

Ibrutinib 420mg (3 x 140-mg capsules) should be taken orally once daily with the first dose taken on day 0 of treatment. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and patients should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the trial (Appendix 10). The use of Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) are prohibited for patients receiving ibrutinib (Appendix 10).

- Patients who have a delay in administration of a dose of the study drug of <6 hours should take the planned dose as soon as possible after the intended time of administration. If the delay in administration of study drug is ≥6 hours, the dose should be skipped. Study drug administration may continue the next day at the usual time but the missed dose should not be made up.
- Vomited Ibrutinib doses may be retaken, but only if the capsule is visible in the vomit.
- If a patient experiences an ibrutinib overdose, consideration should be given as to whether ibrutinib administration should be temporarily interrupted. If the overdose ingestion is recent and substantial, use of gastric lavage or induction of emesis may be considered. Observation for any symptomatic side effects should be instituted, and biochemical and haematological parameters should be followed closely. Appropriate supportive management to mitigate adverse effects should be initiated.

Dose modifications and delays for ibrutinib are detailed in Section 7.4.1. Precautions for use are detailed in Section 7.8.

7.1.2 Obinutuzumab treatment

In patients who are ibrutinib naïve, ibrutinib 420mg/day should be started on Day 0 (24 hours before commencing obinutuzumab) to help reduce potential infusion reactions.

For monitoring of certain AEs, such as TLS, the results of the local haematology and biochemistry should be assessed by a delegated Investigator prior to subsequent infusion.

The most frequently observed AE in patients receiving obinutuzumab were IRRs which occurred predominantly during infusion of the first 1000 mg. In order to mitigate this, **appropriate premedication must be given (see Section 7.6.2).**

Dose modifications and delays for obinutuzumab are detailed in Section 7.4.2. Precautions for use are detailed in Section 7.9.

The initial dose of obinutuzumab should be split in accordance with the scheduled stipulated below (see also Table 1):

Cycle 1

Two infusion bags should be prepared for the infusion on Days 1 and 2 (100 mg for Day 1 and 900 mg for Day 2).. These will then be given as follows:

Day 1: 100 mg obinutuzumab intravenous infusion

- Administered at 25 mg per hour over 4 hours
- For the first dose given on day 1, if the first dose is completed without modifications of the infusion rate or interruptions, the second dose can be administered on the same day (as specified in Day 1 (continued) in Table 1 below)
- Appropriate time, conditions and medical supervision should be available throughout the infusion
- If there are any modifications of the infusion rate or interruptions during the first 100 mg the second dose must be administered the following day

Day 2: 900 mg obinutuzumab intravenous infusion (if not previously given on day 1)

- Administered at 50 mg per hour. In the absence of any infusion related reactions or hypersensitivity, the rate of infusion may be escalated in increments of 50 mg per hour every 30 minutes to a maximum rate of 400 mg per hour

Days 8 and 15: 1000 mg Obinutuzumab intravenous infusion

- Infusions may start at a rate of 100mg per hour and increase by 100mg/hr increments every 30 minutes to a maximum rate of 400mg per hour

Cycles 2-6

Days 29, 57, 85, 113 and 141

- All subsequent cycles will consist of one dose on the first day of the 28 day cycle

In the absence of any infusion related reactions or hypersensitivity, the rate of infusion for the administration of obinutuzumab in all subsequent cycles may start at a rate of 100 mg per hour and increased by 100 mg per hour increments every 30 minutes to a maximum rate of 400 mg per hour

Table 1: Obinutuzumab Schedule

<table>
<tr><th colspan="2">Day of Treatment Cycle</th><th>Dose of Obinutuzumab</th><th>Rate of infusion
(In the absence of infusion reactions/ hypersensitivity during previous infusions)[a]</th></tr>
<tr><td rowspan="4">Cycle1</td><td>Day 1</td><td>100 mg</td><td>Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.</td></tr>
<tr><td>Day 2 or Day 1 (continued)</td><td>900 mg</td><td>If no infusion related reaction occurred during the prior infusion administer at 50 mg/hr.
The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
If the patient experienced an IRR during the previous infusion, start with administration at 25 mg/hr. The rate of infusion can be escalated in increments up to 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.</td></tr>
<tr><td>Day 8</td><td>1000 mg</td><td rowspan="3">If no infusion related reaction occurred during the prior infusion, when the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr
If the patient experienced an IRR during the previous infusion administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.</td></tr>
<tr><td>Day 15</td><td>1000 mg</td></tr>
<tr><td>Cycles 2-6</td><td>Day 1</td><td>1000 mg</td></tr>
</table>

[a] If an infusion reaction occurs, refer to Table 5 in Section 7.4.2.

Monitoring patients for Tumour Lysis Syndrome - Please refer to section 7.9.2 for further guidance

Patients with a high tumour burden, high circulating absolute lymphocyte counts (greater than 25 x 10^9/L) or renal impairment (creatinine clearance of < 70ml/min) are considered at risk of TLS and should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g., allopurinol) or suitable alternatives such as a urate oxidase (e.g., rasburicase), prior to the start of obinutuzumab infusion as per standard local practice. During the first cycles of obinutuzumab treatment, monitor the biochemistry of patients considered at risk for TLS. Should any early signs of TLS be detected, please treat the patient as per local practice.

Monitoring patients for thrombocytopenia

Patients who have a creatinine clearance of between 30 and 50 mL/min at baseline are at greater risk of developing thrombocytopenia. Clinics must perform full blood counts and biochemistry assessments before infusion, directly after infusion and the following morning after infusion

Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Please refer to section 7.9.2 for further guidance.

Should any early signs of thrombocytopenia be detected, please treat the patient as per local practice.

7.2 Assessments

Following informed consent, patients will be required in clinic at the times described in the Assessment Schedule (see Section 5.3 for screening and 7.2.2 for treatment)

Please note that for cohort (B)ii only the Day 0 assessment is arranged as below:

- Physical examination and central and local samples should be taken pre-ibrutinib treatment. The first dose should be on either a Monday or Tuesday to allow for sample delivery
- Central samples should be taken four hours post-ibrutinib administration

For all cohorts, on Day 1, (24 hrs post 1st dose), the blood sample should be taken before the patient begins the obinutuzumab infusion.

Every effort should be made to adhere to the protocol scheduled visits. Visits from months 1 onwards should be scheduled as close as possible but may be scheduled within +/- 7 days. HMDS assessments at other points:

- Following detection of MRD negativity, assessment times will change. Please see Section 7.2.3)
- If there is a clinical need for an additional bone marrow examination—e.g. to identify cause of cytopenia —please send the sample to HMDS for analysis (see section 7.3)

7.2.1 Details of assessments during treatment

Physical examinations:

- Blood pressure
- Pulse
- Temperature
- Weight
- ECOG performance status

A physical examination of the disease should also be included in each clinical assessment, this involves:

- Lymph node disease: the size of the largest lymph nodes in each nodal area (cervical, axillary and inguinal) should be measured in centimetres in 2-dimensions.
- Liver and spleen: If palpable, size of liver and spleen below costal margin should be measured

Constitutional symptom assessment:

- Assessment of B symptoms: fatigue, unintentional weight loss, fevers and night sweats.

Local Laboratory tests:

Haematology

- Haemoglobin
- Lymphocyte count
- Neutrophil count
- Platelet count
- Reticulocyte count
- White blood cell count (with differential count)

Biochemistry

- Albumin
- Alkaline Phosphatase (ALP)
- ALT or AST
- Calcium (adjusted)
- Creatinine
- eGFR
- LDH
- Phosphate
- Potassium
- Sodium
- Total Bilirubin
- Total Protein
- Urea
- Urate

Immunology:

- Direct coombs test
- Serum immunoglobulins and electrophoresis
- β_2 microglobulin concentration

CT scans:

- CT scan of the thorax, abdomen and pelvis should be performed to assess lymph node disease

CT scans will be performed locally at IcICLLe trial sites and reports may be requested for central review by members of the TMG. Redacted reports (where the patient is identified only by TNO) will be requested by email.

ECG

- 12 lead ECG should be performed to assess patients for signs of atrial fibrillation at Month 1 of treatment.

7.2.2 Assessment schedule

Day 0 pre-ibrutinib treatment (cohort (B)ii only)

- Samples for central analysis
  - Peripheral blood sample 4 x 5 mL in EDTA
- Local laboratory tests
- Complete physical examination

Day 0 4 hrs post 1st ibrutinib treatment (cohort (B)ii only)

- Samples for central analysis
  - Peripheral blood 2 x 5mL in EDTA
- Local laboratory tests
- Local immunology

Day 1 (before the 1st obinutuzumab treatment)

- Samples for central analysis:
  - Peripheral blood 2 x 5mL in EDTA
- Complete physical examination
- Local laboratory tests

Day 2

- Samples for central analysis:
  - Peripheral blood 2 x 5mL in EDTA
- Complete physical examination

- Local laboratory tests

Day 8 and Day 15

- Samples for central analysis:
  - Peripheral blood 2 x 5mL in EDTA
- Local laboratory tests

Month 1

- Samples for central analysis (bone marrow samples not required for IcICLLe patients who have transitioned to the Extension Study):
  - Peripheral blood 4 x 5mL in EDTA
  - Bone Marrow Aspirate (EDTA)
  - Bone Marrow Trephine Biopsy (directly in formalin)
- Complete physical examination
- Constitutional symptom assessment
- ECG
- Local laboratory tests
- Disease Response according to modified IWCLL criteria (Appendix 1 & 2)

Month 3

- Samples for central analysis:
  - Peripheral blood 2 x 5mL in EDTA
- Complete physical examination
- Local laboratory tests
- CT scan

Month 6

Cohort (A) and B(i) (IcICLLe):

- Samples for central analysis:
  - Peripheral blood 4 x 5mL in EDTA
  - Bone Marrow Aspirate (EDTA)
  - Bone Marrow Trephine Biopsy (directly in formalin)
- Disease Response according to modified IWCLL criteria (Appendix 1 & 2)

Cohort (B)ii & (B)iii (IcICLLe Extension Study):

- Samples for central analysis
  - Peripheral blood 2 x 5mL in EDTA

All Cohorts

- Complete physical examination
- Constitutional symptom assessment
- Local laboratory
- Local immunology
- CT scan: should only be performed if the result of the 3 month scan was abnormal.

Month 9

Cohort (A) and (B)i (IcICLLe):

- Samples for central analysis:
  - Peripheral blood 2 x 5mL in EDTA

Cohort (B)ii & (B)iii (IcICLLe Extension Study):

- Samples for central analysis:
  - Peripheral blood 4 x 5mL in EDTA
  - Bone Marrow Aspirate (EDTA)
  - Bone Marrow Trephine Biopsy (directly in formalin)
- Disease Response according to modified IWCLL criteria (Appendix 1 & 2)

All Cohorts

- Complete physical examination
- Local laboratory tests

Month 12 and every 6 months thereafter

- Samples for central analysis:
    - Peripheral blood 2 x 5mL in EDTA
- Complete physical examination
- Local laboratory tests

7.2.3 MRD negative remission (all patients)

Assessments to confirm MRD negative remission

All patients will receive treatment on IcICLLe until MRD negativity has been confirmed or until disease progression, whichever is earliest. Confirmation of complete MRD negativity is given by the HMDS once MRD negativity has been recorded for 6 months.

As per IWCLL guidelines, (refer to Appendix 1 for these guidelines and references), MRD negativity should be measured by three consecutive MRD negative peripheral blood (PB) results at 3 month intervals. To confirm the remission 6 months after the first MRD negative PB sample, a bone marrow (BM) examination should be performed with the third blood sample, both PB and BM aspirate should be sent to the HMDS for analysis of the MRD level.

At 6 months following clinical complete remission or the first MRD negative peripheral blood result (as described above), the following assessments should be undertaken to confirm the remission.

- Samples for central analysis:
    - Peripheral blood 4 x 5mL in EDTA
    - Bone Marrow Aspirate (EDTA)
    - Bone Marrow Trephine Biopsy (directly in formalin)
- Complete physical examination
- Constitutional symptom assessment
- CT-scan should be performed to confirm clinical complete MRD negative remission.
- Local blood biochemistry and haematology
- Local Immunology

If the bone marrow does not confirm MRD negativity, the patient should continue to receive ibrutinib/ obinutuzumab until disease progression.

Should a patient be confirmed to be in MRD-negative remission by the bone marrow examination, trial treatment will cease according to the MRD negative remission stopping rules (7.2.3.1). At the end of the extended treatment period defined by the stopping rules, we would strongly recommend that a BM sample is sent with a PB sample to HMDS 2-4 weeks prior to the scheduled stopping date for ibrutinib to confirm the level of continued MRD response.

Subsequently, a patient in MRD-negative remission should be monitored by peripheral blood samples taken every 6 months and sent to HMDS for analysis. During this monitoring period an optional BM sample may be requested to confirm PB results.

7.2.3.1 MRD negative remission stopping rules

MRD will be measured in the peripheral blood and bone marrow at the time-points described in section 7.2.3 above. The MRD negative confirmation date is defined as the date of the first MRD negative peripheral blood (PB) sample. MRD negative status must be confirmed by subsequent PB and bone marrow (BM) assessment within 6 months of the first MRD negative sample.

Patients receiving treatment on IcICLLe who become MRD negative will stop therapy as described below. MRD monitoring will continue according to the trial visit schedule.

Patients receiving ibrutinib + obinutuzumab

- If PB is MRD negative **during** the 6 cycles of obinutuzumab treatment, and MRD negative remission is confirmed by PB and BM assessment, the participant will receive 12 months further ibrutinib from the end of obinutuzumab treatment. If the patient remains MRD negative after these 12 months of further treatment, ibrutinib will be stopped.
- If PB is MRD negative **after** the 6 cycles of obinutuzumab, and MRD negative remission is confirmed by PB and BM assessment, patients will receive further ibrutinib treatment to double the duration of ibrutinib treatment[15] from the first MRD negative PB sample. If the patient is still MRD negative at the end of this extra treatment time, ibrutinib will be stopped.

  For example:

  - If the patient has their first MRD negative blood sample at 9 months, the patient will receive 9 months further ibrutinib treatment: 18 months in total.

Patients receiving ibrutinib monotherapy

- If PB is MRD negative after 12-18 months of ibrutinib treatment, and MRD negative remission is confirmed by PB and BM assessment, patients will receive further ibrutinib to double the duration of treatment from start of ibrutinib to the first MRD negative sample. If the patient remains MRD negative in the PB after this period of treatment, ibrutinib will be stopped.

  For example:

  - If the patient has their first MRD negative blood sample at 12 months, the patient will receive 12 months further ibrutinib treatment: 24 months in total.
  - If the patient is confirmed MRD negative with a BM at 15 months, the patient will receive 15 months further ibrutinib treatment: 30 months in total.
- If PB is MRD negative at or after 24 months ibrutinib treatment, and MRD negative remission is confirmed by PB and BM assessment, a further 18 months of ibrutinib will be given from the first MRD negative sample. If the patient is still MRD negative in the PB at the end of the 18 months further ibrutinib treatment, ibrutinib will be stopped.

7.2.3.2 MRD analysis reports from HMDS

The following diagnostic categories will be used on HMDS reports to define MRD status:

- B-cell chronic lymphocytic leukaemia (B-cell CLL)
  - Applies to cases with high levels of residual disease: more than 5 x 10/9/l circulating CLL cells or 30% CLL cells in the BM,
- B-cell CLL – MRD-positive at iwCLL threshold (≥0.01%)
  - Applies to cases with residual disease detectable at or above the iwCLL 0.01% threshold and so not to be considered for treatment cessation.
- B-cell CLL – MRD-negative at iwCLL threshold (<0.01%)
  - Applies to cases eligible for stopping rules, either with no detectable residual disease or with very low levels of detectable disease below 0.01%.
- Other diagnoses, e.g. “see comments” or “inadequate sample”
  - Applies to cases in which the MRD status cannot be determined at the 0.01% threshold. Interpretation of cases with such a diagnosis should be reviewed by the CI and the Clinical Coordinators.

7.2.4 Assessments at disease progression

Patients will be evaluated at disease progression. Disease progression will be defined using the Modified IWCLL Response Criteria (2008) given in Appendix 2.

Progressive disease during or after any period of therapy is characterised by at least one of the following:

- Lymphadenopathy

[15] Defined as months from date of registration to the Extension Study

- An increase in the liver or spleen size by 50% or more and the *de novo* appearance of hepatomegaly or splenomegaly.
- An increase in the number of blood lymphocytes by 50% or more with at least 5 x 10^9/L B lymphocytes (not before at least 12 months of therapy when the lymphocytosis is expected and is treatment related).
- Transformation to a more aggressive histology (e.g., Richter syndrome). Whenever possible this diagnosis should be established by lymph node biopsy.
- Occurrence of cytopenia (neutropenia, anaemia, or thrombocytopenia) attributable to CLL.

The following assessments should be undertaken:

- Samples for central analysis:
    - Peripheral blood 4 x 5mL in EDTA
    - Bone Marrow Aspirate (EDTA)
    - Bone Marrow Trephine Biopsy (directly in formalin)
- Complete physical examination
- Constitutional symptom assessment
- CT-scan Local blood biochemistry and haematology
- Local immunology

7.3 Sample Collection

All bone marrow biopsies and aspirate should be sent to the Haematological Malignancy Diagnostic Service (HMDS) for analysis. If additional samples are taken for diagnostic purposes at time points not specified for the IcICLLe study please also send these to HMDS for analysis where possible.

Following informed consent, the following samples will be taken for flow cytometry and histological analysis and sent to the HMDS for analysis.

Samples must be taken and sent on Mondays and Tuesdays only.[16] They should be put in the post before 2 pm on the same day of collection, to arrive at the HMDS within 24 hrs (address in section 7.3.1)

Pre-paid Royal Mail Special Delivery Safeboxes will be supplied to sites to ensure that samples can be tracked and will reach HMDS within 24 hours of the sample being taken.

For example, ibrutinib should be taken on day 0 around 10 am. 4 hours after this administration, bloods will be taken (2 pm) and be put into the post to arrive at the HMDS within 24 hours. All samples sent to the HMDS should be accompanied by a completed sample request form. Sites should retain the original Sample Request Forms in the ISF and send a copy with the samples to HMDS.

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to conform to the General Data Protection Regulation (GDPR) 2018.

Biological samples collected from patients as part of this study will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act.

Please refer to the sample collection guidelines for more information.

If the patient's ibrutinib/obinutuzumab treatment is held or delayed, please contact the Trials Office in relation to possible changes to timings of sample collections.

[16] Day 2 of treatment may fall on a Wednesday or Thursday (Extension Study patients only); in this circumstance it is permissible to send samples on that day. If there are any issues surrounding sample collection dates please contact the IcICLLe trial office for help and advice.

7.3.1 HMDS address

Haematological Malignancy Diagnostic Service
Level 3, Bexley Wing
St. James's University Hospital
Beckett Street
Leeds, LS9 7TF

7.3.2 Sample Collection Tables

Table 2: Initial Phase Cohort (A) and (B)i sample collection:

		Peripheral Blood			First-pull bone marrow aspirate		Trephine Biopsy
		4 x 5mL EDTA		2 x 5mL EDTA	0.5 - 2mL EDTA		
	Sample time point ID	1		3	4		6
2 weeks pre-treatment (screening)	A	X			X		X
Day 1: Pre-treatment	B	X					
Day 1: 4 hours after first dose	C			X			
Day 2: 24 hrs after first dose	D			X			
Week 1	E			X			
Week 2	F			X			
Month 1	G	X			X		X
Month 2	H			X			
Month 6	I	X			X		X
Month 9	J			X			
Month 12	K			X			
6 monthly monitoring	L			X			
6 months after clinical or MRD(-)ve remission	MRD	X			X		X
Disease progression	DP	X			X		X
Any other time - i.e. query on cytopenia	QUE	X			X		X

Table 3: Extension Study Cohort (B)ii and (B)iii sample collection

		Extension Study					
		Peripheral Blood			First-pull bone marrow aspirate		Trephine Biopsy
		4 x 5mL EDTA		2 x 5mL EDTA	0.5 - 2mL EDTA		
	Sample time point ID	1		3	4		6
2 weeks pre-treatment (screening)	A	X			X		X
Day 0: Pre ibrutinib treatment	B	X					
Day 0: 4 hours post ibrutinib treatment	C			X			
Day 1: Pre obinutuzumab treatment	D			X			
Day 2	E			X			
Week 1	F			X			
Week 2	G			X			
Month 1	H	X			X		X
Month 3	I			X			
Month 6	J			X			
Month 9	K	X			X		X
Month 12	L			X			
6 monthly monitoring	M			X			
6 months after clinical or MRD(-)ve remission	MRD	X			X		X
Disease progression	DP	X			X		X
Any other time - i.e. query on cytopenia	QUE	X			X		X

7.4 Dose Modifications

Dose delays and modifications should be recorded in the patient's notes and entered onto the appropriate IcICLLe treatment form.

7.4.1 Ibrutinib

Recommendations for Ibrutinib dose modifications are provided in Table 4; variations from these recommendations may be warranted based on an investigator's individual judgment in considering potential risks, benefits, and therapeutic alternatives available to each subject.

The ibrutinib dose should be withheld for any unmanageable, potentially drug-related toxicity that is Grade 3 or higher in severity. Any other clinically important events where dose delays may be considered appropriate by the Investigator must be discussed with the clinical coordinator via the trials office.

Ibrutinib may be withheld for a maximum of 28 consecutive days for toxicity. Study treatment should be discontinued in the event of a toxicity lasting more than 28 days.

The dose of ibrutinib should be modified according to the dose modification guidelines in Table 4 if any of the following toxicities occur:

- Grade 4 neutropenia (0.5 x 10^9/L) for more than 7 days. The use of neutrophil growth factors is permitted.
- Grade 3 thrombocytopenia (50 x 10^9/L) for subjects with normal platelet count at baseline; or, for subjects with baseline thrombocytopenia, a platelet decrease of 50% to 74% from baseline in the presence of significant bleeding.
- Grade 4 thrombocytopenia (25 x 10^9/L); or for subjects with baseline thrombocytopenia, a platelet decrease of ≥75% from baseline or <20 x 10^9/L, whichever is higher.
- Grade 3 or 4 nausea, vomiting, or diarrhoea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy.
- Any other Grade 4 toxicity
- Any unmanageable Grade 3 toxicity

Table 4: Recommendations for ibrutinib dose modifications

Events	Occurrence	Action to be Taken
Grade 2 cardiac failure	First	Withhold until recovery to ≤Grade 1 or baseline; may restart at 280 mg daily
	Second	Withhold until recovery to ≤Grade 1 or baseline; may restart at 140 mg daily
	Third	Discontinue
Grade 3 cardiac arrhythmias	First	Withhold until recovery to ≤Grade 1 or baseline; may restart at 280 mg daily
	Second	Discontinue
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	Discontinue
Grade 3 or 4 non-haematological toxicities Grade 3 or 4 neutropenia with infection or fever Grade 4 haematological toxicities	First	Withhold until recovery to ≤Grade 1 or baseline; may restart at original dose level
	Second	Withhold until recovery to ≤Grade 1 or baseline; may restart at 1 dose level lower (280 mg per day)
	Third	Withhold until recovery to ≤Grade 1 or baseline; may restart at 1 dose level lower (140 mg per day)
	Fourth	Discontinue

At the Investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction.

Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of screening (Child- Pugh class B or C) are excluded from study participation.. Concomitant use of strong CYP inhibitors is not permitted in subjects with chronic hepatic impairment. For subjects with existing chronic mild hepatic impairment (Child-Pugh class A) at enrolment, the starting dose has to be adjusted to a level of 280 mg daily (two capsules). For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib is to a level of 280 mg daily (two capsules). For subjects who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better. Subjects who develop acute hepatic toxicity with liver enzymes Grade 3 or higher while on study should be managed per standard dose modification guidelines in Section 7.4.

7.4.2 Obinutuzumab Dose Modifications

Dosage modifications during treatment (all indications)

No dose reductions of obinutuzumab are recommended. Dose delays should be considered in case of severe or life-threatening neutropenia or thrombocytopenia. For management of symptomatic adverse events (including IRRs), please refer to Table 5 below

Table 5: Infusion rate modification guidelines for infusion related reactions (IRRs)

Grade 4 (life threatening)	Stop infusion and discontinue therapy.
Grade 3 (severe)	Temporarily interrupt infusion and treat symptoms. Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if participant does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (Section 7.1.2). For CLL patients receiving the Cycle 1, Day 1 dose split over 2 days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further. If the patient experiences a second occurrence of a Grade 3 IRR, stop infusion and permanently discontinue therapy.
Grade 1-2 (mild and moderate)	Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion and, if participant does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (Section 10.5).

	For CLL patients receiving the Cycle 1, Day 1 dose split over 2 days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.

Patients should not receive further obinutuzumab infusions if they experience:

- acute life-threatening respiratory symptoms,
- a Grade 4 (i.e., life-threatening) IRR or,
- a second occurrence of a Grade 3 (prolonged/recurrent) IRR (after resuming the
- first infusion or during a subsequent infusion)

7.4.3 Management of obinutuzumab delays

Treatment with obinutuzumab may be discontinued due to poor tolerability/toxicity at the discretion of the treating physician. For patients with evidence of TLS, drug should be discontinued and the patient treated as clinically indicated. Following complete resolution of TLS complications, the study drug may be re-administered at the full dose during the next infusion in conjunction with prophylactic therapy.

a**) Haematological Toxicity**

Thrombocytopenia: Special Considerations

- Patients treated with concomitant medication which could possibly worsen thrombocytopenia related events may be at greater risk of bleeding. Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia.

- Participants who experience G3/4 thrombocytopenia (<25.0 -50 x 10^9 /L) should be closely monitored and transfusion of blood products at the discretion of the treating clinician.

Neutropenia

- For participants who experience G3/4 neutropenia (<0.5 -1.0 x 10^9 /L), we recommend treatment with G-CSF and to delay obinutuzumab until the neutrophils are back above 0.5 x 10^9 /L

b) Non-Haematological Toxicity

- If hypersensitivity to obinutuzumab occurs (typically occurring after previous exposure to obinutuzumab), the infusion should be stopped and treatment permanently discontinued. Participants with a known IgE mediated hypersensitivity to obinutuzumab should not be treated.
- Obinutuzumab should not be administered in the presence of a severe infection.
- Prophylactic therapy aimed at preventing a recurrence of a diagnosed infection should be instituted if clinically indicated.

c) Progressive multifocal leukoencephalopathy (PML)

- Cases of PML have been reported in patients treated with anti-CD20 antibodies including obinutuzumab.
- Treatment with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in the event of a confirmed diagnosis.

d) Infusion Related Reactions

- If a participant develops hypotension during obinutuzumab IV infusions, the withholding of antihypertensive treatments should be considered at the discretion of the treating clinician for

12 hours prior to and throughout obinutuzumab infusions and for the first hour after administration.

7.5 IcICLLe Drug Supply, Labelling and Accountability

7.5.1 Drug Products (IMPs)

Ibrutinib

Ibrutinib is presented for oral administration as hard gelatine capsules containing 140 mg of Ibrutinib and will be supplied free of charge by Pharmacyclics.

Obinutuzumab

Obinutuzumab is provided as a single 1000 mg dose liquid concentrate with a strength of 25 mg/mL. It is supplied in 50 mL glass vials containing 40 mL of the 25 mg/mL liquid concentrate and will be supplied free of charge by F. Hoffman-La Roche Ltd for patients registered to the extension study. Refer to the appropriate IB and pharmacy manual for further details.

7.5.2 Labelling and Storage

Ibrutinib

Ibrutinib capsules are packaged in high-density polyethylene bottles with an induction seal and a child resistant screw-top cap. All packs will be provided fully labelled to comply with the relevant regulations.

Bottles containing capsules of ibrutinib should be stored at controlled room temperature of 15 -25 ^{0}C

Sufficient study drug will be provided for each study period at the beginning of the period. Multiple bottles may be dispensed at a single visit. Capsules should be dispensed in the original bottles provided. Further details can be found in the pharmacy manual.

Obinutuzumab

The recommended storage conditions for obinutuzumab drug product are between 2^{0}C and 8^{0}C and should be protected from light. For clinical formulation-specific and batch-specific instructions, and information on in-use stability, see the packaging label. Please refer to the pharmacy manual and SPC for further information on the storage and handling of obinutuzumab.

7.5.3 Treatment compliance and accountability

Ibrutinib should be retrieved from each patient at the end of each dispensing interval. The quantity of study drug and the date returned by the patient should be recorded on the patient specific drug accountability log. The details of the obinutuzumab prescribed and administered to each patient should also be recorded on the patient specific drug accountability log.

Depending upon the decision of the pharmaceutical company, remaining unused study drug supply will be returned to the supplier after the study is completed or will be discarded or destroyed at the clinical site. If the study drug is discarded or destroyed at the clinical site, standard institutional policy should be followed. Records documenting the date of study drug shipping or destruction, relevant lot numbers, and amount shipped or destroyed should be maintained.

In addition, all patients will be issued with a Patient Diary at each visit as necessary for the whole time they are on treatment. Patients will be asked to complete the diary, recording the time that each dose was taken, and whether any doses were missed. The diary also includes a section where the patient can record any relevant information such as side effects suffered or reasons for missed doses. The completed diary will be collected by the centre at clinic visits and returned to the IcICLLe Study Office.

Further details of supply, labelling and accountability can be found in the IcICLLe pharmacy manual.

7.6 Supportive Treatment

Ibrutinib Premedication **Prophylactic treatment against infection with co-trimoxazole and acyclovir is mandated for patients in receipt of ibrutinib therapy**.

No other specific premedications or supporting medications are required in conjunction with ibrutinib administration.

Supportive medications in accordance with standard practice (such as for emesis, diarrhoea, etc.) are permitted. The hematopoietic growth factors filgrastim and pegfilgrastim are allowed. Transfusions may be given in accordance with institutional policy.

Subjects with high tumour burden prior to treatment are considered to be at increased risk of tumour lysis syndrome:

Such subjects should be considered for hydration and treatment to prevent tumour lysis as per local practice prior to study treatment, as well as frequent monitoring of associated signs and symptoms.

7.6.1 Obinutuzumab Premedication

Obinutuzumab premedications should be reported to the investigator and recorded in the Case Report Form (CRF).

Prophylactic treatment against infection with co-trimoxazole and acyclovir is <u>mandated</u> for patients in receipt of ibrutinib and obinutuzumab combination therapy.

Patients with a high circulating lymphocyte count (> 25 x 10^9/L) and/or renal impairment (CrCl < 70 mL/min) are considered at risk of TLS and should receive prophylaxis. They must receive treatment with uricostatics (e.g. allopurinol or adequate alternative) and hydration starting 12-24 hours prior to the infusion of obinutuzumab, as well as frequent monitoring of associated signs and symptoms. Corticosteroid premedication is mandatory for CLL patients in the first cycle. Premedication for subsequent infusions and other premedication should be administered as described below.

Please refer to Table 7 for premedications to reduce the risk of IRRs.

<u>Table 7:</u> Obinutuzumab premedications

Cycle Day of Treatment	Patients requiring premedication	Premedication	Administration
Cycle 1: Day 1	All patients	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion.
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion
		Anti-histaminic drug[3]	
Cycle 1: Day 2	All patients	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion.
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion
		Anti-histaminic drug[3]	
All subsequent infusions	Patients with no IRR during the previous infusion	Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion
	Patients with an IRR (Grade 1 or 2) with the previous infusion	Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion
		Anti-histaminic drug[3]	
	Patients with a Grade 3 IRR with the previous infusion OR patients with lymphocyte counts >25 x 10^9/L prior to next treatment	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion.
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion
		Anti-histaminic drug[3]	

[1] 100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone, hydrocortisone should not be used as it has not been effective in reducing rates of IRR.

[2] e.g. 1000 mg acetaminophen/paracetamol

[3] e.g. 50 mg diphenhydramine

7.7 Concomitant Medication

To the extent possible, administration of any prescription or over-the-counter drug products other than study medication should be minimised during the study period. Subjects should be discouraged from use of herbal remedies, tobacco products, or excessive alcohol at any time during the clinical study.

If considered necessary for the subject's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator.

Subjects should be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the-counter, or illicit) before and during the course of the study. Any concomitant drugs taken by a subject during the course of the study and for 30 days post the last dose of study treatment should be recorded in the medical record and the CRF with the reason for use.

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REFER TO APPENDIX 10 FOR A LIST OF CAUTIONED AND PROHIBITED MEDICATION.

7.7.1 Prohibited concomitant medications

- Warfarin
- Any chemotherapy, anticancer immunotherapy, corticosteroids (at doses equivalent to prednisone >20 mg per day), experimental therapy, or radiotherapy are prohibited while the patient is receiving ibrutinib treatment.
- Vaccination with live vaccines
- Both ibrutinib and obinutuzumab are contraindicated in patients with clinically significant hypersensitivity to the compound itself or to its excipients
- ACE inhibitors and ARBs

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances for which prohibited therapies are administered.

Please consult with the CI and Clinical Coordinators via the trials office if unsure about the use of a specific drug.

7.7.2 Concomitant Medications to be Used With Caution with ibrutinib

Agents that may increase ibrutinib plasma concentrations:

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong CYP3A4 or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

If a strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, or cobicistat) must be used, reduce ibrutinib dose to 140 mg for the duration of the inhibitor use or withhold treatment temporarily (for 7 days or less).. Subjects should be monitored for signs of ibrutinib toxicity.

If a moderate CYP3A inhibitor (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, or dronedarone) must be used, reduce ibrutinib to 280 mg for the duration of the inhibitor use. Avoid grapefruit and Seville oranges during ibrutinib/placebo treatment, as these contain moderate inhibitors of CYP3A

No dose adjustment is required in combination with mild inhibitors.

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in Appendix 10. A comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

For the most comprehensive effect of CYP3A inhibitors or inducers on ibrutinib exposure, please refer to the current version of the IB.

Agents that may decrease ibrutinib plasma concentrations:

Administration of ibrutinib with inducers of CYP3A4 can decrease ibrutinib plasma concentrations.

Co-administration of ibrutinib with strong CYP3A inducers, rifampin, in healthy subjects decrease ibrutinib plasma concentrations by approximately 10-fold. Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

If the benefit outweighs the risk and a strong or moderate CYP3A4 inducer must be used, monitor patient closely for lack of efficacy (see sections 4.3 and 4.4). Mild inducers may be used concomitantly with ibrutinib, However, patients should be monitored for potential lack of efficacy. As ibrutinib solubility is pH dependent, there is a theoretical risk that medicinal products increasing stomach pH (e.g. proton pump inhibitors) may decrease ibrutinib exposure.

A list of common CYP3A inhibitors or inducers is provided in Appendix 10.

Drugs That May Have Their Plasma Concentrations Altered by ibrutinib

In vitro studies carried out by Pharmacyclics indicated that ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 and does not display time-dependent CYP450 inhibition. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak inducers of CYP450 isoenzymes *in vitro*. Therefore, it is unlikely that ibrutinib has any clinically relevant drug-drug interactions with drugs that may be metabolized by the CYP450 enzymes.

In vitro studies indicated that ibrutinib is not a substrate of P-gp, but is a mild inhibitor. Ibrutinib is not expected to have systemic drug- drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There are no clinical data available, therefore co-administration of narrow therapeutic index P-gp substrates (e.g., digoxin) with ibrutinib may increase their blood concentration and should be used with caution. Patients monitored closely for toxicity.

QT Prolonging agents

Any medications known to cause QT prolongation should be used with caution; periodic monitoring with ECGs and electrolytes should be considered and if needed, a medical monitor may be contacted.

Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, corticosteroids (at doses equivalent to prednisone >20 mg per day), experimental therapy, or radiotherapy are prohibited while the subject is receiving ibrutinib treatment. Short courses (<14 days) of treatment for non-cancer-related medical reasons (treatment for autoimmune cytopenias are permitted) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted.

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib.

Erythropoietic growth factors (eg, erythropoietin), platelet growth factors (eg, thrombopoietin), and sagramostim are also prohibited.

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances which prohibited therapies are administered.

7.7.3 Concomitant Medications and Obinutuzumab

No formal drug-drug interaction studies have been performed, although limited drug interaction sub-studies have been undertaken for obinutuzumab with bendamustine, CHOP (cyclophosphamide,

doxorubicin, vincristine, prednisolone), and FC (fludarabine, cyclophosphamide) and chlorambucil. Co-administration with obinutuzumab had no effect on the pharmacokinetics of bendamustine, FC, chlorambucil or the individual components of CHOP; in addition, there were no apparent effects of bendamustine, FC, chlorambucil or CHOP on the pharmacokinetics of obinutuzumab. A risk for interactions with concomitantly used medicinal products cannot be excluded.
Immunisation with live or attenuated viral vaccines, following obinutuzumab treatment has also not been studied, therefore the vaccination with live vaccines is not recommended during treatment and until B-cell recovery.

7.8 Precautions for ibrutinib use

7.8.1 Antiplatelet Agents, Anticoagulants and Bleeding Related Events

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. Subjects requiring the initiation of therapeutic anticoagulation therapy (e.g., atrial fibrillation),.. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

Patients participating in IcICLLe will be monitored closely for haemorrhagic adverse events. Ibrutinib should be held at least 3 to7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding (see section 7.8.3).

7.8.2 Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose.

There is no specific experience in the management of ibrutinib overdose in patients. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

7.8.3 Guidelines for ibrutinib management with surgeries or procedures

Ibrutinib may increase the risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while on study.

- For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
- For minor procedures (i.e. such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

7.8.4 Treatment related lymphocytosis

Similar to other agents targeting B-cell receptor signalling, transient lymphocytosis is a pharmacodynamic effect of ibrutinib, in which the inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of tumour cells to the peripheral blood (Stevenson 2011).

Upon initiation of treatment, a transient phase of increase in lymphocyte counts (i.e., ≥50% increase from baseline and above absolute count 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most patients (75%) with relapsed/refractory CLL/SLL treated with ibrutinib. This effect has also been observed in some patients (33%) with relapsed/refractory MCL treated with ibrutinib. This observed transient lymphocytosis is usually not associated with an adverse event and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and resolves within a median of 18.7 weeks in CLL patients. A large increase in the number of circulating lymphocytes (eg, >400,000/mcL) has been observed in some subjects.

7.8.5 Leukostasis

A substantial increase in the number of circulating lymphocytes (e.g., > 400,000/mcL) has been observed in a subset of patients. There have been isolated cases of leukostasis reported in patients treated with ibrutinib.

A high number of circulating malignant cells (>400000/mcL) may confer increased risk; these patients should be closely monitored. Administer supportive care such as hydration and/or leukophoresis as indicated. Ibrutinib may be temporarily held. The sponsor must be notified of any instances where ibrutinib is held.

7.8.6 Cardiac arrhythmia and cardiac failure

Atrial fibrillation, atrial flutter, ventricular tachyarrhythmia and cardiac failure have been reported in patients treated with ibrutinib, particularly in patients with acute infection or cardiac risk factors including hypertension, diabetes mellitus , and a previous history of atrial fibrillation/cardiac arrhythmia. Fatal and serious cardiac arrhythmias or cardiac failure have occurred in patients treated with ibrutinib. Patients with significant cardiac comorbidities may be at greater risk of events, including

sudden fatal cardiac events.

Periodically monitor all patients clinically for cardiac arrythmia. Patients who develop arrhythmic symptoms or new onset of dyspnoea, dizziness or fainting should be evaluated clinically and if indicated have an electrocardiogram (ECG) performed.

In patients who develop signs and/or symptoms of ventricular tachyarrhythmia, ibrutinib should be temporarily discontinued and a thorough clinical benefit/risk assessment should be performed before possibly restarting therapy. In patients with pre-existing atrial fibrillation requiring anticoagulant therapy, alternative treatment options to ibrutinib should be considered. In patients who develop atrial fibrillation on therapy with ibrutinib a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk and where alternatives to ibrutinib are non-suitable, tightly controlled treatment with anticoagulants should be considered.

7.8.7 Tumour lysis syndrome

Tumour lysis syndrome has been reported with ibrutinib therapy. Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Monitor patients closely and take appropriate precautions.

7.8.8 Rash

Mild to moderate rashes have been observed with ibrutinib alone or in combination with other drugs. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

7.8.9 Stevens-Johnson Syndrome (SJS)

A single case of SJS was reported in a male subject with CLL treated with ibrutinib 420 mg/day. The subject was also receiving multiple concomitant medications known to be associated with SJS. Subjects should be monitored closely for signs and symptoms suggestive of SJS.

7.8.10 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anaemia) were reported in subjects treated with ibrutinib.

7.8.11 Diarrhoea

Approximately one-third of subjects treated with ibrutinib monotherapy and two-thirds treated with combination therapy reported diarrhoea. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe, with only a small number of Grade 3 events, and no Grade 4 events reported to date.

These events are rarely severe and are generally managed with supportive therapies including anti-diarrhoeals and anti-emetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as Clostridium difficile or other infectious agents. Should symptoms be severe or prolonged, ibrutinib treatment should be modified as directed in the individual protocols.

7.8.12 Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these infections have been associated with hospitalization and death.

Cases of progressive Multifocal Leukoencephalopathy (PML) including fatal ones have been reported following the use of ibrutinib within the context of a prior or concomitant immunosuppressive therapy. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms. If PML is suspected then appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded. If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments should be considered.

7.8.13 Second Primary Malignancies

Other malignancies, most frequently skin cancers, have occurred in subjects treated with ibrutinib.

7.8.14 Non-melanoma skin cancer

Non-melanoma skin cancers were reported in patients treated with ibrutinib than in patients treated with comparators in pooled comparative randomised phase 3 studies. Monitor patients for the appearance of non-melanoma skin cancer.

7.8.15 Interstitial lung disease

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Randomized, controlled Phase 3 studies did not show an increased incidence rate of ILD in subjects treated with ibrutinib as compared to subjects treated with active control. Subjects should be monitored and evaluated for symptoms (e.g., dyspnoea, cough or pyrexia) and treated symptomatically, including interruption of the suspected agent as appropriate. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines.

7.8.16 Hypertension and ACE inhibitors/ARBs

In a recently published paper[6] it is cited that 'ibrutinib is associated with dramatic efficacy against B-cell malignancies. Yet, ibrutinib has been linked with potentially-limiting cardiotoxicity, including emerging reports of profound hypertension'. The key points highlighted in this paper are as follows:

'1) Among lymphoid malignancy patients treated with ibrutinib, the subsequent incidence of new hypertension is nearly 72%.

2) Development of new or worsened hypertension following ibrutinib initiation associates with a more than two-fold increased risk of other cardiac events.'

It was identified during an interim analysis of the FLAIR study, that participants with pre-existing hypertension or cardiac co-morbidities randomised to ibrutinib + rituximab had an elevated risk of sudden unexplained death or cardiac death which appears to be associated predominantly with ACE inhibitors. Since ARBs target the same pathway as ACE inhibitors then these may be considered to also be a potential risk.

ACE inhibitors and ARBs are therefore prohibited for participants receiving ibrutinib. For participants requiring antihypertensive therapy an alternative therapy should be given.

Common examples of ACE inhibitors used for the treatment of hypertension include (but not limited to) Ramipril, Perindopril, Lisinopril and Enalapril. Common examples of ARBs include (but not limited to) Valsartan, Losartan, Candesartan and Irbesartan. Please see Appendix 10 for a more complete list of ACE inhibitors and ARBs.

7.8.17 Cerebrovascular Accidents

Although causality has not been established, cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of ibrutinib in the post-marketing setting, with and without concomitant atrial fibrillation and/or hypertension. Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended.

7.9 Precautions for obinutuzumab use

7.9.1 Infusion-Related Reactions

The most frequently observed AEs in patients receiving obinutuzumab were IRRs which occurred predominantly during infusion of the first 1000mg. IRRs may be related to cytokine release syndrome which has also been reported in patients treated with obinutuzumab. Since some patients may develop hypersensitivity or other IRRs to obinutuzumab, premedications are listed in Section 7.6.2 and these mitigation measures should be followed.

Hypotension may occur during obinutuzumab intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medication.

Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period.

Since some patients may develop hypersensitivity or other IRRs to obinutuzumab, premedications are listed in Section 7.6.2.

For patients with a high lymphocyte count or bulky lymphadenopathy, the infusion may be given extremely slowly over a longer period of time, or the dose may be split and given over more than one day. Of note, the risk factors predicting an IRR with the first infusion are still unconfirmed and there is no clear correlation between tumour mass (circulating disease or lymph nodes) and incidence of IRR.

7.9.2 Tumour Lysis Syndrome

Tumour Lysis Syndrome (TLS), including fatal TLS, has been reported with obinutuzumab. Please refer to section 7.1.2 for details on the risk of TLS.

Table 8: Definition of laboratory and clinical TLS

Metabolic Abnormality	Criteria for Classification of laboratory Tumor Lysis Syndrome[a]	Criteria for Classification of clinical Tumor Lysis Syndrome[a]
Hyperuricemia	Uric acid > 8.0 mg/dL (475.8 µmol/L) in adults, or above the upper limit of the age appropriate normal range in children	
Hyperphosphatemia	Phosphorus > 4.5 mg/dL (1.5 mmol/L) in adults or > 6.5 mg/dL (2.1 mmol/L) in children	
Hyperkalaemia	Potassium > 6.0 mmol/L	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalaemia

Hypocalcaemia	Corrected calcium < 7.0 mg/ dL (1.75 mmol/L) or ionized calcium < 1.12 mg/dL (0.3 mmol/L)b	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypo-tension, or heart failure probably or definitely caused by hypocalcaemia
Acute kidney injury[c]		Increase in serum creatinine level of 0.3 mg/dL (26.5 µmol/L; or a single value > 1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria (average urine output of < 0.5 mL/kg/hr for 6 hr)

[a]. For laboratory tumour lysis syndrome, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days prior to the start of therapy or up to 7 days afterwards. Clinical tumour lysis syndrome requires the presence of laboratory tumour lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

[b.] The corrected calcium level in mg/dL = measured calcium level in mg/dL + 0.8 x (4-albumin in g/dL).

[c]. Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg/dL (26.5 µmol/L) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumour lysis syndrome.

Patients who are considered to be at risk of TLS [e.g. patients with a high tumour burden or a high circulating lymphocyte count (>25 x10^9/L) and/or renal impairment (CrCl < 70 mL/min)] should receive adequate tumour lysis prophylaxis with uricostatics (e.g. allopurinol or adequate alternative) and hydration starting 12-24 hours prior to the infusion of obinutuzumab. All patients considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

7.9.3 Thrombocytopenia

Severe and life threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with obinutuzumab. Fatal haemorrhagic events have also been reported in patients treated with obinutuzumab. It seems that the first cycle is the greatest risk of haemorrhage in obinutuzumab -treated patients. A clear relationship between thrombocytopenia and haemorrhagic events has not been established. Patients treated with concomitant medication, which could possibly worsen thrombocytopenia related events such as platelet inhibitors and anticoagulants, may be at greater risk of bleeding. Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e. platelet transfusion) according to institutional practice is at the discretion of the treating physician.

7.9.4 Neutropenia

Cases of Grade 3 or 4 neutropenia, including febrile neutropenia, have been reported with obinutuzumab administration. Grade 3 or 4 neutropenia has predominantly been observed in patients with CLL. Patients who experience Grade 3 or 4 neutropenia should be monitored until neutrophil values return to at least Grade 2. If treatment is necessary it should be administered in accordance with local guidelines and the administration of G-CSF should be considered.

It is strongly recommended that patients with severe and long lasting (>1 week) neutropenia receive antimicrobial prophylaxis throughout the treatment period until resolution to Grade 1 or 2. Antiviral and antifungal prophylaxis should be considered. Cases of late onset neutropenia (occurring 28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) have also been reported. Patients with renal impairment (CrCl < 50 mL/min) are more at risk of neutropenia

7.9.5 G-CSF Administration

For patients with neutropenia, G-CSF should be administered as per the American Society of Clinical Oncology (ASCO) guidelines or institutional guidelines.

7.9.6 Risk of Infection including Hepatitis B reactivation and Progressive Multifocal Leukoencephalopathy

Obinutuzumab has been associated with an increased risk of infections so should not be administered in the presence of active severe infections. Physicians should exercise caution when treating patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections. Particular attention should be given to patients who have had significant prior immunosuppressive treatment, such as high-dose chemotherapy or a stem cell transplant. Signs and/or symptoms of infection should result in prompt evaluation and appropriate samples for bacteriological investigation prior to starting antibiotic or other treatment.

Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with Obinutuzmaub). Physicians should be aware of symptoms suggestive of progressive multifocal leukoencephalopathy (PML) and consider the diagnosis in any patient presenting with new-onset or changes to pre-existing neurologic manifestations. The symptoms of PML are nonspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g. muscular weakness, paralysis and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as “cortical” (e.g. aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture. Therapy with Obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the evaluation and treatment of PML.

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with anti-CD20 antibodies including Obinutuzumab. Hepatitis B virus screening should be performed in all patients before initiation of treatment with Obinutuzumab. At a minimum this should include hepatitis B surface antigen (HBsAg) status and hepatitis B core antibody (HBcAb) status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with Obinutuzumab.

7.9.7 Immunisation

The safety of immunisation with live or attenuated viral vaccines following obinutuzumab therapy has not been studied and vaccination with live virus vaccines is not recommended during treatment and until B cell recovery.

7.9.8 Gastrointestinal Perforation

GI perforation is an important identified risk of obinutuzumab. GI tract involvement is much more frequent in patients with NHL than in patients with CLL. Rapid tumour lysis can lead to GI perforation, with potential serious outcomes. Causes of GI perforation other than cancer therapy are spontaneous perforation secondary to tumour (either primary or metastatic), iatrogenic perforation secondary to instrumentation (endoscopy) or infections. Cases of GI perforation have been reported in patients treated with obinutuzumab, mainly in patients with NHL. Patients with GI involvement should be monitored for signs of GI perforation.

7.9.9 Worsening of pre-existing cardiac conditions

In patients with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with obinutuzumab. These events may occur as part of an IRR and can be fatal. Therefore patients with a history of cardiac disease should be monitored closely. In addition these patients should be hydrated with caution in order to prevent a potential fluid overload.

7.9.10 Hypersensitivity reactions including anaphylaxis

Anaphylaxis has been reported in patients treated with Gazyvaro. Hypersensitivity may be difficult to distinguish from IRRs. If a hypersensitivity reaction is suspected during infusion (e.g. symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion must be stopped and treatment permanently discontinued. Patients with known IgE mediated hypersensitivity to obinutuzumab must not be treated.

7.10 Patient Follow Up

All patients will remain on study treatment for at least 12 months unless their disease progresses or the patient achieves clinical complete remission or MRD-negative remission according to the modified IWCLL Response Criteria. Guidance for patients achieving an MRD-negative remission is given in Section 7.2.3.

After they have received ibrutinib treatment for a minimum of 6 months, patients in the relapsed/refractory IcICLLe cohort (B(i)) may be given the option to continue treatment via the IcICLLe extension study.

Patients in the treatment naïve cohort of IcICLLe who have stable disease or have maintained a response will remain on Ibrutinib treatment, with the cost of ibrutinib paid for by collaborating pharmaceutical company, until disease progression or confirmed MRD negative remission.

All patients will be followed up for trial outcome measures until death.

7.11 Patient Discontinuation and Withdrawal

7.11.1 For ibrutinib: Discontinuation from Study Drug

Patients may discontinue study treatment at any time. However every reasonable effort should be made to keep each patient on the treatment. Patients who stop treatment due to adverse experiences (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 CRF.

The following are justifiable reasons for the Investigator to discontinue a patient from study treatment:

- Unacceptable toxicity
- Progressive disease as defined by the Modified IWCLL Response Criteria (revised 2008) (Appendix 2)
- Unforeseen events: any event which in the judgement of the Investigator makes further treatment inadvisable
- SAE requiring discontinuation of treatment
- Withdrawal of consent for treatment
- Serious violation of the study protocol (including persistent patient attendance failure and persistent non-compliance)
- Pregnancy
- Discontinuation by the Investigator for clinical reasons not related to the study drug treatment

If a patient discontinued/withdraws from study treatment, an assessment 30 days after the last dose of ibrutinib will be performed, if possible. This is to include a physical examination, blood samples and an assessment of AEs. Concomitant medication will also be recorded.

Patients may also withdraw from study procedures/follow-up schedule. In this case data about their disease status and other treatments will still be collected at routine visits. All the results of the evaluations and observations, together with a description of the reasons for study discontinuation, must be recorded in the CRF.

7.11.2 For obinutuzumab: Discontinuation from Study Drug

Patients must discontinue study drug if they experience any of the following:

- Pregnancy
- PML

- Anaphylaxis, acute respiratory distress; prolonged or recurrent infusion reactions.
- Grade 4 IRR: Patient should be withdrawn immediately and treatment must be discontinued permanently
- Grade 3 IRR at re-challenge despite adequate premedication: Patient must be withdrawn immediately and treatment must be discontinued permanently
- Grade 3 or 4 neutropenia or thrombocytopenia as defined by the Modified IWCLL Response Criteria (revised 2008) (Appendix 2), that has not resolved to Grade ≤ 2 and requires a treatment delay to the next Cycle, Day 1 dose by 4 weeks
- Grade ≥ 2 non-haematological toxicity that does not resolve to Grade ≤1/baseline and requires a treatment delay to the next Cycle, Day 1 dose by 4 weeks

Patients may also withdraw from all aspects of study participation including data collection.

Any patient who discontinues either study drug may continue ibrutinib or obinutuzumab monotherapy at the discretion of the clinician.

8. ADVERSE EVENT REPORTING

The collection and reporting of AEs will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed in Appendix 4.

The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the Investigator Brochure.

8.1 Reporting Requirements

8.1.1 Adverse Events

All medical occurrences which meet the definition of an AE (see Appendix 4 for definition) should be reported. Please note this does not include abnormal laboratory findings. An abnormal laboratory value is only considered to be an AE if the abnormality:

- Results in early discontinuation from the study treatment and/or
- Requires study drug dose modification or interruption, any other therapeutic intervention or is judged to be of significant clinical importance

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded. Pre-existing conditions should only be reported if the condition worsens by at least 1 CTCAE grade. Asymptomatic treatment-related lymphocytosis should also not be considered an AE. Subjects with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures. Details of all AEs experienced by the patient should be recorded in the hospital notes.

8.1.2 Serious Adverse Events

Investigators should report AEs that meet the definition of an SAE (see Appendix 4 for definition).

8.1.3 Monitoring pregnancies for potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.

In the event that a patient or their partner becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient's details) and return to the trials office within 24 hours of becoming aware. If it is the patient who is pregnant provide outcome data on a follow-up Pregnancy Notification Form. Where the patient's partner is pregnant consent must first be obtained and the patient should be given a pregnancy release of information form to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy they should sign the pregnancy release of information form. Once consent has been obtained provide details of the outcome of the pregnancy on a follow-up Pregnancy Notification Form. If appropriate also complete an SAE Form as detailed below.

8.1.4 Reporting period

Details of all AEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment (refer to Treatment Schedule A and B).

8.2 Reporting Procedure

8.2.1 Site

8.2.1.1 Adverse Events

AEs should be reported on an AE Form (and where applicable on an SAE Form). An AE Form should be completed at each visit and returned to the Trials Office.

AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see Appendix 5). Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of: (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

8.2.1.2 Adverse Events of Special Interest (AESI) Ibrutinib

The following list of specific adverse events will be assessed as part of standard safety monitoring activities by Pharmacyclics. These events should be reported to the trial office as SAEs within 24 hours of awareness following the procedure detailed in section 8.2.1.3. All events of special interest should be submitted on the SAE form within 24 hours of awareness even if they do not meet serious criteria.

Major Haemorrhage

In order for an event to qualify as a major haemorrhage, it must include ANY one of the following criteria:

- Any treatment-emergent haemorrhagic adverse event of Grade 3 or higher. All haemorrhagic events requiring a transfusion of red blood cells should be reported as Grade 3 or higher per CTCAE.
- Any treatment emergent serious adverse event of bleeding of any grade.
- Any treatment emergent central nervous system haemorrhage/hematoma of any grade.
- This definition is the recommendation provided by the Subcommittee on Control of Anticoagulation of the Scientific and standardisation Committee of the International Society on Thrombosis and haemostasis (Schulman 2005).

Intracranial Haemorrhage

Any intracranial haemorrhage adverse event, including subdural hematoma/haemorrhage, epidural haematoma/haemorrhage and intracerebral haemorrhage, of any grade severity.

8.2.1.3 Adverse Events of Special Interest (AESI) Obinutuzumab

The following types of events are considered by the Sponsor to be “AEs of special interest” (AESIs) due to their observed frequency and/or clinical relevance:

- AEs associated with obinutuzumab infusion (defined as any AE considered as related to obinutuzumab occurring during or within 24 hours of an obinutuzumab infusion and meets the seriousness criteria
- Infections fulfilling the criteria of seriousness
- Neutropenia fulfilling the criteria of seriousness
- Tumour Lysis Syndrome

8.2.1.4 Other Malignancies

In addition to all routine AE reporting, all new malignant tumours including solid tumours, skin malignancies and haematological malignancies are to be reported for the duration of study treatment and during the specified follow-up period.

8.2.1.5 Serious Adverse Events

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in the Investigator Site File (ISF).

AEs defined as serious and which require reporting as an SAE should be reported on an SAE Form.

When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.03.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be sent to the Trials Office using the contact details listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE email the SAE Form to:

reg@trials.bham.ac.uk and CC IcICLLe@trials.bham.ac.uk

On receipt the Trials Office will allocate each SAE a unique reference number. This number will be sent back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the Trials Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE.

For SAE Forms completed by someone other than the Investigator the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the Trials Office in the post and a copy kept in the ISF.

Investigators should also report SAEs to their own Trust in accordance with local practice.

8.2.1.6 Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

8.2.2 Trials Office

On receipt of an SAE form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the Reference Safety Information) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

8.2.3 Reporting to the Competent Authority and main Research Ethics Committee

8.2.3.1 Suspected Unexpected Serious Adverse Reactions

The Trials Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and main Research Ethics Committee (REC) within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days.

8.2.3.2 Serious Adverse Reactions

The Trials Office will report details of all SARs (including SUSARs) to the MHRA and main REC annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

8.2.3.3 Adverse Events

Details of all AEs will be reported to the MHRA on request.

8.2.3.4 Other safety issues identified during the course of the trial

The MHRA and main REC will be notified immediately if a significant safety issue is identified during the course of the trial.

8.2.4 Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

8.2.5 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

8.2.6 Manufacturer of Investigational Medicinal Product

All SAEs will be reported to the manufacturer of the Investigational Medicinal Products as guidelines set out in the research grant and supply agreement.

9. DATA HANDLING AND RECORD KEEPING

9.1 Data Collection

The Case Report Form (CRF) will comprise a set of forms capturing details of eligibility, baseline characteristics, treatment and outcome details etc., and will be provided to the Site at the time of initiation.

The CRF must be completed, signed/dated and returned to the Trials Office by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the timeframe specified into the CRF completion guidelines. The exceptions to this are the SAE Form and Withdrawal Form which must be co-signed by the Investigator.

Entries on the CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. Missing and ambiguous data will be queried. All sections are to be completed before returning. Quality of Life questionnaires do not require recording on the CRF and should be forwarded to the Trials Office upon completion.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

The completed originals should be sent to the Trials Office and a copy filed in the Investigator Site File.

Trial forms may be amended by the Trials Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

9.2 Archiving

It is the responsibility of the Principle Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, patients' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 10 years after the end of the trial or following the processing of all biological material collected for research, whichever is the later. Do not destroy any documents without prior approval from the CRCTU Document Storage Manager.

10. QUALITY MANAGEMENT

10.1 Site Set-up and Initiation

All sites will be required to sign a Clinical Study Site Agreement prior to participation. In addition all participating Investigators will be asked to sign the necessary agreements, registration forms and supply a current CV to the Trials Office. All members of the site research team will also be required to sign the Site Signature and Delegation Log, which should be returned to the Trials Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File and a Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Trials Office must be informed immediately of any change in the site research team.

10.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the CRCTU Quality Management Plan. Additional on-site monitoring visits may be triggered for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required the Trials Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the IcICLLe trial staff access to source documents as requested.

10.3 Central Monitoring

Where a patient has given explicit consent sites are requested to send in copies of signed Informed Consent Forms for in-house review.

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming Case Report Forms for compliance with the protocol, data consistency, missing data and timing. Sites will be sent Data Clarification Forms requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group and Data Monitoring Committee and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the main Research Ethics Committee (REC) and the Medicines for Healthcare products Regulatory Agency (MHRA).

10.4 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are also requested to notify the Trials Office of any MHRA inspections.

10.5 Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, 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

Sites are therefore requested to notify the Trials Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

11. END OF TRIAL DEFINITION

The trial end date is deemed to be 6 months after the last patient has completed the protocol defined interventional treatment. This will allow sufficient time for the completion of protocol procedures, data collection and data input.

The Trials Office will notify the MHRA and REC that the trial has ended at the appropriate time and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

Sites should continue to notify the Trials Office of changes in Principal Investigator by completing and returning (where required) an Investigator Registration Form together with a current signed and dated CV until otherwise notified.

12. STATISTICAL CONSIDERATIONS

12.1 Definition of Outcome Measures

12.1.1 Primary Objectives / Outcome Measures

- Proportion of patients achieving MRD-negative remission by IWCLL criteria (depletion of CLL below 0.01% in the peripheral blood and bone marrow) in a) the initial phase of the study at or before the 6 month assessment and b) the Extension Study at or before the 9 month assessment. Independent decisions will be made for each study (initial and extension).

12.1.2 Secondary Objectives / Outcome Measures

- Best disease response, whether complete remission (CR), complete remission with incomplete marrow recovery (Cri) or partial remission (PR), to treatment in a) the initial phase of the study at or before the 6 month assessment and b) the Extension Study at or before the 9 month assessment. Independent decisions will be made for each study (initial and extension)., assessed according to the IWCLL Criteria (revised 2008) (Appendix 1). The dynamics of response will be assessed both in terms of the change in absolute levels of CLL in the blood and marrow as well as the changes in the proliferating compartment and changes in chemokine receptor.
- 1 and 2 year progression free survival for relapsed/refractory and treatment naïve patients defined as time from date of registration to date of progression (per the modified 2008 IWCLL criteria) or death from any cause. Alive patients who are progression free will be censored at their date of last follow-up.
- 1 and 5 year overall survival for relapsed/refractory and treatment naïve patients is defined as the time from date of registration to the date of death from any cause.
- Toxicity of ibrutinib and obinutuzumab
- CLL cell levels as a percentage of total leucocytes in the bone marrow (BM) and absolute counts in the peripheral blood (PB).
- The proportion of patients with >5%, 0.5-5%, <0.5% CLL cells in cell cycle (expressing Ki67) in the peripheral blood and bone marrow in a) the initial phase of the study at or before the 6 month assessment and b) the Extension Study at or before the 9 month assessment
- Change in the expression levels of CD10, CD103, CD11c, CD185, CD196, CD20, CD200, CD22, CD23, CD25, CD27, CD305, CD31, CD38, CD39, CD43, CD49d, CD5, CD79b, CD81, CD95, IgD, IgG, or IgM on CLL cells relative to baseline by more than 50% and at least 500 arbitrary units in median fluorescence intensity.

12.1.3 Exploratory outcome measures

- Change in phosphoprotein expression (including Akt, Syk, MAPK, ERK and Btk) at screening in CLL cells stimulated with immunoglobulin in the presence and absence of *in vitro* ibrutinib and during/after treatment in CLL cells stimulated with immunoglobulin measured as fluorescence intensity in arbitrary units relative to unstimulated cells/control.
- Assessment of the mechanism of response and resistance to ibrutinib in patients with lack of or failure to maintain a response or disease progression compared to those patients with good responses (mutation analysis of key BCR pathway genes, gene expression profiling and epigenetic modifications)
- Response correlated with secondary prognostic markers (such as FISH, IGHV, CD38/CD49d expression)
- Change in the expression levels of BCL2, IRF4, ZAP70, CD62L, CD184, CD80, CD40, CD11a, CD54, CD154, CCR7, CD24, CD86 on CLL cells relative to baseline by more than 50% and at least 500 arbitrary units in median fluorescence intensity.
- The absolute numbers and proportions of CD4+ and CD8+ T-cell subsets with respect to expression of CD27, CD62L, CD45RA, CCR4 and CXCR3.
- Assessment of MRD levels using novel technologies including high throughput sequencing

Data on outcome measures will be collected as stipulated in the protocol of this feasibility study to confirm the mechanism of action of ibrutinib/obinutuzumab. Results from this trial will then inform the design of a randomised phase II trial using response as the primary outcome measure to determine whether ibrutinib/obinutuzumab shows sufficient evidence of activity in these cohorts of patients.

12.2 Analysis of Outcome Measures

12.2.1 IcICLLe (initial phase)

Statistical analysis in this study, will be based on descriptive statistics only.

The primary endpoint is the dichotomous variable, MRD Negativity. The precise specification for determining whether a patient is MRD-negative is detailed in section 7.2.3

The number and proportion of patients in each response category will be reported with 95% confidence interval and presented as a proportion of the total number of patients recruited to this study.

- The number and proportion of patients experiencing any grade haematological and non-haematological toxicities will be reported as a proportion of the number of patients recruited.
- Survival estimates will be calculated using the method of Kaplan and Meier, and point estimates reported with 95% CIs.
- The number and proportion of patients with abnormalities in chromosome 11 or 17, or with an unmutated IGHV gene will be reported.

12.2.2 IcICLLe Extension Study

The primary endpoint is the dichotomous variable, MRD Negativity. The precise specification for determining whether a patient is MRD-negative is detailed in section 7.2.3.

We will judge the rate of activity of the experimental regimen using this outcome measure. Under Ibrutinib alone, we would expect a negligible proportion of patients to become MRD-negative. We will regard the combined regimen as worthy of further clinical investigation in a larger, randomised trial if we find reasonable evidence that the rate of activity exceeds 20%.

We will analyse the activity rate of MRD Negativity using a Bayesian method. With binomial data, we can express our prior beliefs on activity using a Beta distribution and use the conjugacy property to express our posterior beliefs as another Beta distribution.

The experimental regimen has not been investigated before so we have no strong prior information. As such, we will use a weakly-informative prior. This is achieved using a Beta(1, 1) distribution, equivalent to saying a-priori that we consider no activity rate to be any more or less likely than any other. After n patients have completed treatment, r of whom become MRD-negative, our posterior beliefs about the activity rate will described by a Beta($1+r$, $1+n-r$) distribution. At the end of the trial, we will declare the regimen as showing sufficient activity to warrant further investigation if we are at least 50% confident that the level of activity exceeds 20%. We refer to this as the activity decision rule.

It is possible but not expected that fewer than 40 patients will actually register to this study. For instance, there might be unanticipated and unavoidable shortfalls in recruitment. A benefit of using the Bayesian method is that we will be able to handle deviations from target recruitment in a consistent manner by invoking the Bayesian decision rule described above on the available data.

For all trial sizes between 30 and 40 patients inclusive, the activity decision rule has the following operating characteristics:

- If the true activity rate is 30%, the probability of approving the regimen is always greater than 90%;
- If the true activity rate is 10%, the probability of approving the regimen is always less than 10%;
- The rule never approves the regimen when observing responses in fewer than 18.7% of patients.

It is our intention to invoke the activity decision rule when the target level of recruitment has been achieved and sufficient follow-up has been completed to inform activity status for all patients. If the target level of recruitment is not possible, the decision rule should be invoked on the fullest possible data-set, i.e. after the maximum number of patients have been recruited and followed-up for as long as possible to inform activity status to the greatest extent.

Some illustrations of the activity decision rule are given in Table 8. The variable θ is the activity rate of MRD-negativity.

Table 8: Illustrations of the activity decision rule under different assumed trial outcomes with prior beliefs θ ~ Beta(1,1)

Total Patients, *n*	Patients achieving MRD-negativity, *r*	Posterior Beliefs for θ | *r*,*n*	Prob(θ | *r*,*n* > 0.2)	Decision
40	8	Beta(9, 33)	56.19%	Approve treatment
40	7	Beta(8, 34)	40.69%	Reject treatment
37	7	Beta(8, 31)	50.03%	Approve treatment
35	6	Beta(7, 30)	40.07%	Reject treatment

12.3 Planned Sub Group Analyses

The data from the initial and Extension phases of the study will be analysed separately.

In the initial phase, the two–cohorts, A and B(i), will be analysed separately. The immunoglobulin mutation status (mutated [>98% similarity to germ-line] versus unmutated [>98% similarity to germ-line]) will be analysed separately as will patients with 17p deleted and 11q deleted CLL.

In the extension phase the same analysis applies to the two cohorts B(ii) and B(iii)..

12.4 Timelines for Analysis

The data from the initial and Extension phases of the study will be analysed separately.

In the initial phase the first primary analysis of primary and secondary outcome measures will occur within 3 months of the final patient being assessed for primary outcome. (which is assessed at 6 months of trial treatment)Subsequent final analyses of all outcome measures is planned 2 years after the final patient is registered into the initital phase.

For the extension phase, the first primary analysis of primary and secondary outcome measures will occur within 3 months of the final patient being assessed for primary outcome (which is assessed at 9 months of trial treatment). Subsequent final analyses of all outcome measures is planned 2 years after the final patient is registered to the Extension phase.

12.5 Study Size Calculations

12.5.1 IcICLLe

20 patients per cohort (Ai and Bi), a total of 40 patients recruited to the trial.

Compliance is likely to be high as the treatment is given orally and patients will be monitored closely during the treatment period with regular clinic visits. We also expect the loss to follow-up to be minimal as all patients will need to attend clinics regularly as part of standard practice.

This feasibility study of 40 patients will confirm the mechanism of action of ibrutinib. Results from this trial will then inform the design of a randomised phase III trial using response as the primary outcome measure to determine whether ibrutinib shows sufficient evidence of activity in treatment naïve and relapsed/refractory CLL patients.

12.5.2 IcICLLe Extension Study

Up to 20 relapsed/refractory patients from IcICLLe will transition to the extension study (cohort Biii). At least 20 relapsed/refractory CLL patients not previously treated in the IcICLLe study (ibrutinib naïve, cohort Bii) will be recruited so that the total sample size in the extension study is no more than 40 patients.

12.6 Stopping Guidelines

Stopping rules will serve as guidelines at DMC consultation and are not absolute rules that would result in automatic closure of study recruitment. Clinical judgement is essential in balancing issues of safety and efficacy in light of any new external information.

12.6.1 IcICLLe

Stopping guidelines will be included to allow the trial to terminate early if the treatment is considered too toxic.

For the purposes of these rules, a toxicity is defined as “Any toxicity of grade 3 or greater, considered to have a causal relationship to ibrutinib, that leads to cessation of therapy”. A patient is defined as tolerating treatment if they do not experience a toxicity. Rules are based on a Simon 2-stage design.

Treatment naïve: To continue with the trial and conclude that toxicity levels are acceptable, at least 8 of the first 11 patients need to tolerate treatment (i.e. no more than 3 patients experience a toxicity), and at least 16 patients of the 20 total need to tolerate treatment (i.e. no more than 4 patients experience a toxicity overall). This gives a 95% chance of going to full length and concluding the treatment is not too toxic when toxicity is acceptable (defined as 10% rate), and 77% chance of detecting a problem when it’s too toxic (defined as 30% rate).

Relapse / refract: To continue with the trial and conclude that toxicity levels are acceptable, at least 6 of the first 10 patients need to tolerate treatment (i.e. no more than 4 patients experience a toxicity), and at least 15 patients of the 20 total need to tolerate treatment (i.e. no more than 5 patients experience a toxicity overall). This gives a 93% chance of going to full length and concluding the treatment is not too toxic when toxicity is acceptable (defined as 15% rate), and 75% chance of detecting a problem when it’s too toxic (defined as 35% rate).

12.6.2 Extension Study

Stopping guidelines will be included to allow the trial to terminate early if the treatment is considered too toxic.

For the purposes of these rules, toxicity is defined as “Any toxicity of grade 3 or greater, considered to have a causal relationship to ibrutinib or obinutuzumab, that leads to cessation of therapy”. A patient is defined as tolerating treatment if they do not experience a toxicity. Rules are based on a Simon 2-stage optimal design.

To continue with the trial and conclude that toxicity levels are acceptable, at least 12 of the first 15 patients need to tolerate treatment (i.e. no more than 3 patients experience a toxicity), and at least 30 of the first 36 patients need to tolerate treatment (i.e. no more than 6 patients experience a toxicity). This gives a 90% chance of going to full length and concluding the treatment is not too toxic when toxicity is acceptable (defined as 10% rate) and 95% chance of detecting a problem when it’s too toxic (defined as 30% rate).

13. TRIAL ORGANISATIONAL STRUCTURE

13.1 Sponsor

This trial is sponsored by The University of Birmingham as part of the TAP project.

13.2 Coordinating Centre

The trial is being conducted under the auspices of the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham according to their local procedures.

13.3 Trial Management Group

A Trial Management Group (TMG) will be established and will include the Chief Investigator (Prof Peter Hillmen), Prof Andy Rawstron (co-investigator), other identified clinical collaborators, the Trial Statistician, Senior Trial Coordinator and the Trial Coordinator. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG will be responsible for the day-to-day running and management of the trial and will meet by teleconference or in-person as required.

13.4 Data Monitoring Committee

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further patients. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. During the recruitment phase of the trial the DMC is scheduled to meet one month prior to the due date of the DSUR and annually thereafter. Additional meetings may be called if recruitment is much

faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the Trial Management Group (TMG) who will convey the findings of the DMC to MHRA, funders, and/or sponsors as applicable. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety. The trial would also stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community. Additionally the DMC may stop the trial due to toxicity as per the stopping guidelines detailed in section 12.6.

13.5 Finance

This is a clinician-initiated and clinician-led trial funded by Bloodwise as part of the Trials Acceleration Programme. Pharmacyclics and Roche are also supplying funding and free drug for use in the trial.

No individual per patient payment will be made to NHS Trusts, Investigators or patients.

The trial is part of the NIHR CRN portfolio.

14. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the General Data Protection Regulation and Data Protection Act 2018 and Human Tissue Act 2008) and Good Clinical Practice (GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the main Research Ethics Committee (REC) prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the Trials Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

15. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation and Data Protection Act 2018 for health and care research. The University of Birmingham, as the Sponsor for the IcICLLe study, will be using information from patient medical records in order to undertake this trial and will act as the data controller for the study. This means that the University of Birmingham are responsible for looking after the information and using it properly. University of Birmingham and the NHS will keep identifiable information about the patients for at least 25 years after the study has finished, to allow the results of the study to be verified if needed.

All information collected by the Sponsor will be securely stored at the Trials Office at the University of Birmingham on paper and electronically and will only be accessible by authorised personnel. The only people in the University of Birmingham who will have access to information that identifies a patient will be people who manage the study or audit the data collection process.

The NHS will use the patient`s name and contact details to contact patients about the research study, and make sure that relevant information about the study is recorded for their care, and to oversee the quality of the trial. With the patient`s permission, the research team (at site) will notify the patient`s GP that they intend to participate in the study.

With the patient's consent, their full name (on consent form only), initials and date of birth will be collected at trial entry. The research team (at site) will send a copy of the signed consent form in the post to the Trials Office. This will be used to perform in-house monitoring of the consent process. In routine communication between the hospital and the Trials Office, the patient will only be identified by study number, initials and date of birth. Data may be provided to the Trials Office on paper or electronically.

By taking part in the study, the patient will be agreeing to allow research staff from the Trials Office at the University of Birmingham to look at the study records, including their medical records. It may be necessary to allow authorised personnel from government regulatory agencies (e.g. Medicines and Healthcare products Regulatory Agency (MHRA), the Sponsor and/or NHS bodies to have access to patient medical and research records. This is to ensure that the study is being conducted to the highest possible standards. Anonymised data from the study may also be provided to other third parties (e.g. the manufacturer of the trial treatment) for research, safety monitoring or licensing purposes.

The Investigator must maintain documents not for submission to the Trials Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

16. INSURANCE AND INDEMNITY

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The University of Birmingham cannot offer indemnity for non-negligent harm. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

17. PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Trial Management Group (TMG) and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

18. REFERENCE LIST

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4. O'Brien S, et al. The Bruton's Tyrosine Kinase (BTK) Inhibitor PCI-32765 Induces Durable Responses in Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): Follow-up of a Phase Ib/II Study. *Blood* (ASH Annual Meeting Abstracts) 2011 118: Abstract 983.
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6. Dickerson T, Wiczer T, Waller A, et al, Hypertension and incident cardiovascular events following ibrutinib initiation. Blood 2019 134 (22): 1919 -1928 http://bloodjournal.hematologylibrary.org/blood/article/doi/10.1182/blood.2019000840/375010/Hypertension-and-Incident-Cardiovascular-Events

APPENDIX 1 – IWCLL RESPONSE CRITERIA (REVISED 2008)

For a complete version of the IWCLL Guidelines for the diagnosis and treatment of chronic lymphocytic leukaemia: a report from the International Workshop on Chronic Lymphocytic Leukaemia updating the National Cancer Institute Working Group 1996 guidelines visit:

http://bloodjournal.hematologylibrary.org

Hallek et. al. Blood. 2008 Dec 15;112(13):5259

Definition of response, relapse, and refractory disease

Assessment of response should include a careful physical examination and evaluation of the blood and marrow.

IWCLL Response criteria

Parameter	CR	CRi	PR	SD**	PD
Group A					
Lymphadenopathy	None >1.5 cm	All group A criteria for CR satisfied but reduction in any group B values from CR criteria	Decrease ≥50%*		Increase ≥50% or appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates.
Hepatomegaly	None		Decrease ≥50%		Increase ≥50%
Splenomegaly	None		Decrease ≥50%		Increase ≥50%
Blood lymphocytes	<4000/μL		Decrease ≥50% from baseline		Increase ≥50% from baseline – unless treatment-related lymphocytosis
Bone marrow	Normocellular, <30% lymphocytes, no B-lymphoid nodules.		50% reduction in marrow infiltrate, or B-lymphoid nodules		
Group B					
Platelet count	>100 000/μL		>100 000/μL or increase ≥50% over baseline		Decrease of ≥50% from baseline secondary to CLL
Haemoglobin	>11.0 g/dL		>11.0 g/dL or increase ≥50% over baseline		Decrease of >2 g/dL from baseline secondary to CLL
Neutrophil count	>1500/μL		>1500/μL or >50% improvement over baseline		

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

CR (complete remission): all of the criteria have to be met

PR (partial remission) with leucocytosis: at least two of the criteria of group A plus one of the criteria of group B have to be met;

* 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. In small lymph nodes (<2 cm), an increase of less than 25% is not considered to be significant.

****SD (Stable disease):** is absence of progressive disease (PD) and failure to achieve at least a PR

PD (Progressive disease): at least one of the above criteria of group A or group B has to be met.

CR with incomplete marrow recovery (CRi). A controversial issue is how best to categorize the response of patients who fulfil all the criteria for a CR 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 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 non-cytopenic CR.

APPENDIX 2 – MODIFIED IWCLL RESPONSE CRITERIA (REVISED 2008)

Due to the mode of action of ibrutinib treatment, a modified IWCLL response criteria will also be used to assess patients where a nodal response has occurred but CR or PR criteria have not yet been obtained.

The modified IWCLL response criteria consist of the following changes to the 2008 IWCLL (Appendix1):

Definition of disease progression for participants receiving Ibrutinib

- Ibrutinib may cause blood lymphocytosis with concomitant reduction in lymphadenopathy and/or splenomegaly.
- In this setting an increase in blood lymphocyte counts, by itself, does not indicate an increased tumour burden, but may rather reflect a re-distribution of leukaemia cells from the lymphoid tissues to the blood. In such cases, increased blood lymphocytosis is not a sign of treatment failure or progressive disease. Such a treatment-related lymphocytosis usually occurs within the first few months of initiating therapy with ibrutinib and can be very marked.
- Treatment-related lymphocytosis, for the purposes of this protocol, is defined as an elevation in blood lymphocyte count of >50% compared to baseline and >5 x 10^9/L

APPENDIX 3 - WMA DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Recommendations guiding physicians
in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for

the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. 4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE

(Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN

SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

APPENDIX 4 - DEFINITION OF ADVERSE EVENTS

Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Adverse Reaction

All untoward and unintended responses to an IMP related to any dose administered.

Comment:

An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event

Any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- New Primary Cancer
- Or is otherwise considered medically significant by the Investigator***
- Results in an AE of special interest :

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Serious Adverse Reaction

An Adverse Reaction which also meets the definition of a Serious Adverse Event.

Suspected Unexpected Serious Adverse Reaction

A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.

A SUSAR should meet the definition of an AR, UAR and SAR.

Unexpected Adverse Reaction

An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).

When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.

APPENDIX 5 - COMMON TOXICITY CRITERIA GRADINGS

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The full CTCAE document is available in the Investigator site file and on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

APPENDIX 6 – ECOG PERFORMANCE STATUS

0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

APPENDIX 7 – CLL STAGES

A	Clinical stage A CLL is characterised by no anaemia (Haemoglobin ≥ 10 g/dL) or thrombocytopenia (platelets ≥ 100,000/mm^3) and fewer than three areas of lymphoid involvement (< 3 enlarged areas).
B	Clinical stage B CLL is characterised by no anaemia (Haemoglobin ≥ 10 g/dL) or thrombocytopenia (platelets ≥ 100,000/mm^3) with three or more areas of lymphoid involvement (≥ 3 enlarged areas).
C	Clinical stage C CLL is characterised by anaemia (Haemoglobin ≤ 10 g/dL) and/or thrombocytopenia (platelets < 100,000/mm^3) regardless of the number of areas of lymphoid enlargement (any number of enlarged areas).

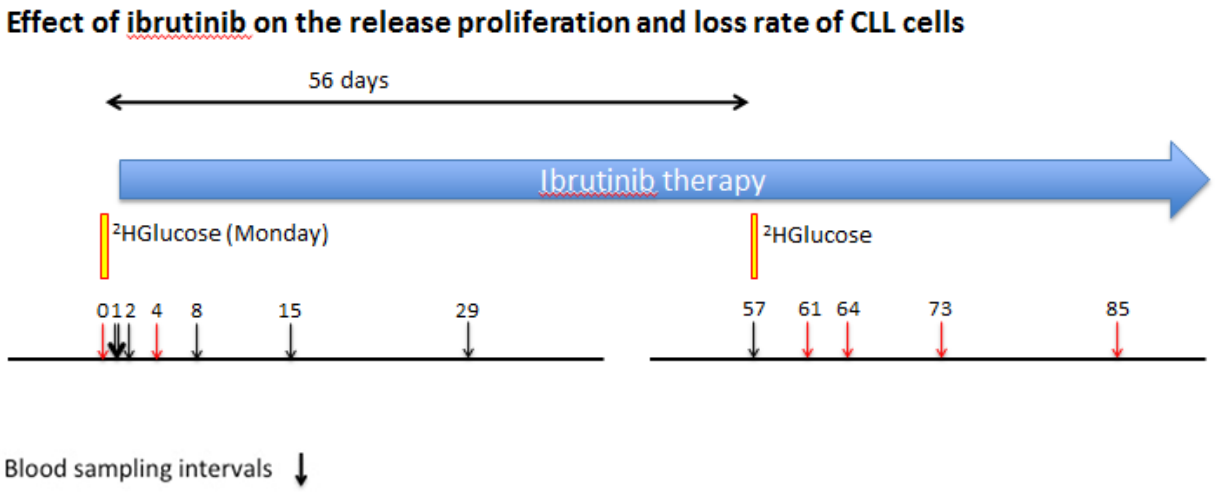
APPENDIX 8 – KINETICS SUB-STUDY

Patients who fulfil the eligibility criteria for the IcICLLe trial may be asked to participate in an optional kinetic assessment study, which will run alongside the IcICLLe trial and will be based at King's College London.

Study Design

The objective of this study is to investigate tumour kinetics during ibrutinib therapy.

Ibrutinib treatment will start on day 1.



Additional visits over and above the basic IcICLLe study are indicated in red

Assessment Schedule – Kinetic Sub-study

	Day (-) 0	Day 1*	Day 2*	Day 4	Day 8*	Day 15*	Day 29*	Day 57*	Day 61	Day 64	Day 73	Day 85
	Start of cycle 1	Ibrutinib treatment starts					Week 4 Start of cycle 2	Week 8				
Blood samples	X	X					X	X	X	X	X	

*The patient is already required to be in clinic on these days for the IcICLLe trial

Investigations:

On day 1 of each labelling (day (-)0) patients will receive deuterated glucose every 30 minutes for 10 hours. A blood sample will be taken before starting and finger prick samples every 1, 3, 5, 8 and 10 hours and on days 1, 2, 4 and 8 to assess deuterated glucose levels.

EDTA blood samples will be taken at the indicated time points. The day 1 sample will be taken immediately before and 4 hours after idelalisib administration. Peripheral blood mononuclear cells will be purified by density centrifugation and cryopreserved in DMSO as viable cells in minimum aliquots of

$2x10^7$. A minimum of 6 aliquots per time point will be stored. A full blood count will also be performed at each time point. Samples will be shipped in batches to Kings College Hospital on dry ice for sorting. Deuterium incorporation into CD19+ and other subsets will be measured in Professor Macallan's laboratory at St Georges Hospital.

Clinic Attendance:

All blood samples to be collected before study drug administration (day 0 to day 1) should ideally be taken at times where samples are required during the screening process, to limit the inconvenience caused to the patient. For blood samples following drug administration, the patient will only be required to attend clinic on five extra occasions – days 4, 61, 64, 73 and 85.

The above scheme is for measuring tumour proliferation and death only. There is the option for patients registered at King's College Hospital London for additional samples to be taken on days 1, 2 and 3 to assess the time of peak release of proliferating cells.

APPENDIX 9 - UK CLL TRIALS BIOBANK

Patients taking part in the IcICLLe study may also be approached to donate samples to the UK CLL Trials Biobank. This is separate research involving tissue sample collection but participation is recommended as it allows researchers to study the underlying biology of CLL and add significant value to this field. This study is sponsored by the University of Liverpool. Patient Information Sheets, Informed Consent Forms and sample collection kits can be obtained directly from Dr Melanie Oates.

ukctbb@liverpool.ac.uk and m.oates@liverpool.ac.uk

UK CLL Trials Biobank

The UK CLL Trials Biobank aims to identify biomarkers that predict therapeutic response to the treatments being evaluated. Patients who consent to the Biobank study are requested to donate saliva, anti-coagulated blood and clotted blood samples before therapy starts. Additional samples are requested throughout the course of the IcICLLe trial, as per the Assessment Schedule table below. These samples will be used for a range of studies of direct relevance to the treatment of CLL.

It should be noted that the UK CLL Trials Biobank is a generic national resource which collects samples from patients taking part in all national CLL trials. As such, it has its own ethical approval for the purposes described above, including Patient Information Sheet and Consent Form, which should be used **in addition** to those provided for the IcICLLe study.

The Biobank study is optional for IcICLLe patients but participation is recommended. Additional samples collected from IcICLLe patients specifically for the Biobank study will be sent to the CLL Biobank for use in future research.

Consent to the UK CLL Trials Biobank

Participation within the UK CLL Trials Biobank should be discussed with patients at the same time as discussing their participation in IcICLLe.

Patients who wish to have biological samples sent to the Biobank should be asked to sign an additional UK CLL Trials Biobank consent form, a copy should be returned to the UK CLL Trials Biobank at Royal Liverpool University Hospital.

Sample Collection

When a patient consents to the Biobank study, please request a sample collection kit directly from the Biobank (email addresses above).

Peripheral blood samples will be collected for the Biobank at regular intervals during the study. The Biobank samples should be taken at the visits specified in the assessment schedule (see table below) using the sample collection kits provided by the Biobank. The samples should be posted to the Biobank on the day of collection, as per the instructions contained in the sample collection kits (not on a Friday).

Assessment Schedule – UK CLL Trials Biobank

	Two weeks prior to treatment	Day 8	1 month	6 months (cohort i)	9 months (cohort ii and iii)	In the event of disease progression
Blood samples	10 mL coagulated 40 mL anticoagulated	10 mL coagulated 20 mL anticoagulated				
Saliva Sample	2 mL saliva					

APPENDIX 10 – CAUTIONED AND PROHIBITED MEDICATION

Some inhibitors of CYP3A4/5 are defined below.

Some cautioned and prohibited medications are listed below. This list is not exhaustive, any new medications should be reviewed with guidance from pharmacy in order to identify potential interactions.

Class of drug	Examples	During trial
Strong inhibitors of CYP3A	Boceprevir, clarithromycin, cobicistat, conivaptan, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir (alone or in combination with one or more of the following: danoprevir, elvitegravir, indinavir, lopinavir, ombitasvir, paritaprevir, saquinavir, tipranavir), telaprevir, telithromycin, troleandomycin, voriconazole. Grapefruit juice, Seville oranges, starfruit.	**Avoid the use of these drugs** If a strong CYP3A inhibitor must be used, reduce ibrutinib dose to 140 mg or withhold treatment for the duration of inhibitor use withhold treatment temporarily (for 7 days or less). Patients should be monitored for signs of ibrutinib toxicity. If the patient must receive these drugs the patient must be monitored for toxicity.
Moderate inhibitors of CYP3A	Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil.	**Avoid the use of these drugs** If a moderate CYP3A inhibitor must be used, reduce ibrutinib dose to 280 mg or withhold treatment for the duration of inhibitor use. Patients should be monitored for signs of ibrutinib toxicity. If the patient must receive these drugs the patient must be monitored for toxicity.
Weak inhibitors of CYP3A	Chlorzoxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, tacrolimus, ticagrelor.	These drugs may be administered and patients should be monitored for any toxicity/lack of efficacy.
Strong inducers of CYP3A	Carbamazepine, enzalutamide, mitotane, phenytoin, rifampicin, St. John's wort.	**Avoid the use of these drugs.** Where use cannot be avoided this should be discussed with the Chief Investigator/Clinical Coordinator via the Trial Office. If the patient must receive these drugs the patient must be monitored for lack of efficacy.

Class of drug	Examples	During trial
Moderate inducers of CYP3A	Bosentan, efavirenz, etravirine, modafinil.	**Avoid the use of these drugs.** Where use cannot be avoided this should be discussed with the Chief Investigator/Clinical Coordinator via the Trial Office. If the patient must receive these drugs the patient must be monitored for lack of efficacy.
Weak inducers of CYP3A	Armodafinil, rufinamide.	**These drugs may be administered and patients should be monitored for any lack of efficacy.**
CYP3A4 substrates sensitive to gut CYP3A metabolism	Dihydroergotamine, ergotamine, fentanyl, cyclosporine, sirolimus and tacrolimus	Based on in vitro data, ibrutinib is a weak reversible inhibitor towards CYP3A4 at the intestinal level and may therefore increase the exposure to CYP3A4 substrates sensitive to gut CYP3A metabolism. No clinical data are available on this interaction. Caution should be exercised if co-administering ibrutinib with CYP3A4 substrates administered orally with narrow therapeutic range
ACE inhibitors	Ramipril, Lisinopril, Perindopril, Enalapril, Fosinopril, Imidapril, Quinapril, Trandolapril, Captopril	**ACE inhibitors are prohibited for patients receiving ibrutinib.** Participants should be moved to an alternative antihypertensive treatment. Where use cannot be avoided, ibrutinib should be stopped and discussed with the Chief Investigator/Clinical Coordinator and the Trial Office.
ARBs	Azilsartan, Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan	**ARBs are inhibitors are prohibited for patients receiving ibrutinib**. Participants should be moved to an alternative antihypertensive treatment. Where use cannot be avoided ibrutinib should be stopped and discussed with the Chief Investigator/Clinical Coordinator and the Trial Office.